Develop New or Improved Approaches for Preventing or Delaying the Onset or Progression of Disease and Disability

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Alcohol Interventions in Trauma Centers: Reducing the Risk of Repeat Injuries

Background: Alcohol abuse and alcoholism are the most common underlying causes of injuries in the U.S. Approximately half of patients admitted to trauma centers are under the influence of alcohol. On average, these patients have blood alcohol concentrations (BACs) that are nearly double the legal limit for driving in most states. Moreover, the majority are chronic alcohol abusers who, without treatment for their alcohol problem, are likely to incur more injuries.

In recent years, a series of randomized trials have shown that health care providers who use "brief interventions" can significantly reduce their patients' alcohol use and related problems, particularly in problem drinkers who are not alcohol-dependent. Brief interventions generally consist of feedback and advice from a health care provider and agreement, by the patient, on a course of action. Studies have shown that brief interventions delivered in primary care settings can decrease alcohol use for at least 1 year in persons who drank above the recommended limits.

Building on the premise that a recent life-threatening injury may make patients more receptive to alcohol counseling, investigators recently conducted the first randomized, prospective, controlled trial on the use of alcohol interventions in a trauma center. The investigators screened trauma center patients for alcohol problems, and the 762 patients who tested positive were assigned to either a control group or a group receiving a single motivational interview with a psychologist trained in the use of brief interventions. The 30-minute interview consisted of feedback about the patients' drinking patterns compared with national norms, their levels of intoxication at admission, and the negative consequences of drinking. The interviewers emphasized the patients' assumption of responsibility for reducing drinking in order to decrease their risk level and offered strategies to assist the patients in changing their drinking behavior. Follow-up interviews were conducted in person or by phone 6 and 12 months later.

Advance: At the 12-month follow-up, the intervention group had 47 percent fewer new injuries requiring treatment in an emergency room or trauma center than did the control group. In addition, the intervention group had decreased alcohol consumption by 22 standard drinks per week, while the control group had decreased drinking by only about 7 drinks per week. The difference in alcohol intake was most pronounced in men (who made up more than 80 percent of the subjects) and in patients with drinking problems in the mild-to-moderate range; no benefit was seen in patients with severe dependence.

Implications: This study capitalizes on the "teachable moment following injury" to show that a simple 30-minute intervention can change critical behavior, reducing both repeat injuries and alcohol consumption levels. The results indicate that the rate of recurring alcohol-related injuries that require emergency care could be cut nearly in half if trauma centers provided routine screening and brief interventions for alcohol problems.

Gentilello LM, Rivara FP, Donovan DM, et al: Alcohol interventions in a trauma center as a means of reducing the risk of injury recurrence. Annals of Surgery, 230(4):473-83. 1999.

Successful Prevention Program Targets Steroid Abuse in High School Athletes

Background: Since the 1950s, some athletes have taken anabolic steroids to build muscles and boost their athletic performance. Increasingly, other segments of the population also have been taking these synthetic substances. The Monitoring the Future study, NIDA's annual survey of drug abuse among middle and high school students across the country, showed a significant increase in anabolic steroid abuse among eighth and tenth graders between 1998 and 1999. In addition, the percentage of 12th-graders who believed that taking these drugs causes "great risk" to health declined from 68 percent to 62 percent.

Advance: Researchers have developed a steroid abuse prevention program, Adolescents Training and Learning to Avoid Steroids (ATLAS), that consists of interactive classroom and training sessions given by peer educators and facilitated by coaches and strength trainers that is showing some promising results. The program was implemented in 31 Oregon high school football teams and included discussion of sports nutrition, exercise alternatives to anabolic steroids and dietary supplements, the effects of drug abuse on sports, drug refusal role playing, and the creation of health promotion messages. An evaluation of the program's effectiveness showed that an athlete's intention to use and actual use of steroids was significantly lower among students who participated in the ATLAS program. At the year follow-up, illicit drug use and alcohol use was reduced. Other long-term effects included fewer students drinking and driving, less use of dietary supplements, and improved nutritional behavior. A program designed for adolescent girls on sports teams, patterned after the program designed for boys, is currently being tested.

Implications: This intervention is the first of its kind designed to reduce the use of anabolic steroids and other drugs in young high school athletes. The use of a team-centered, gender-specific education program is an effective way to reduce student's use of alcohol and other illicit drugs, such as anabolic steroids. School athletic teams provide an optimal environment in which to provide drug prevention and health promotion activities. The development of healthy lifestyle behaviors in young people can result in a lifetime of health promotion and risk reduction behaviors that will pay dividends for the rest of one's life.

Goldberg L, MacKinnon DP, Elliot DL, Moe EL, Clarke G, Cheong J: The adolescents training and learning to avoid steroids program . Archives of Pediatric and Adolescent Medicine, 154(4):332-8. 2000.

School-based Program Reduces Smoking Among Minority Girls

Background: Smoking rates for women and girls have continued to increase despite a growing understanding of the harmful effects of smoking. Historically, smoking rates for minority women have been lower than those of white women; however, in the 1990s smoking among African American and Hispanic adolescents began to increase after several years of decline. In addition, risks from smoking may take a greater toll on minority women. For example, black women are disproportionately affected by hypertension, diabetes, and delivery of low-birth weight infants, health problems that all can be exacerbated by smoking. In order to stem the increase in smoking among minority girls, investigators tailored a 15-session smoking prevention program (found previously successful for white youth) to 7th grade minority girls in 29 inner-city schools. The researchers modified the language and examples used to illustrate concepts, and situations for the specific target population. This intervention focused on the development of social resistance skills and personal and social competence development. In addition, a booster session was given in 8th grade.

Advance: The researchers found that girls who participated in the smoking cessation program were less likely to initiate smoking if they had not previously smoked when compared to girls who did not participate in the intervention. Experimental smokers in the intervention group were less likely than those in the non-intervention group to escalate to monthly smoking, even if they had begun smoking before participating in the program. Participants had lower levels of intentions to smoke, more accurate perceptions of peer and adult smoking behaviors, better refusal skills, and reported fewer risk behaviors. Researchers also found that the data confirmed the effectiveness of having a school-based and teacher-led program.

Implications: With smoking-related diseases claiming the lives of more than 430,000 Americans each year, it is critical that we continue to seek ways to reduce smoking and its initiation, particularly among minority youth who may be at higher risk for smoking-related health problems if they continue to smoke. This study showed that smoking initiation in minority, inner-city girls can be reduced by a school-based prevention strategy. Prior to this study limited evidence existed showing that school-based prevention efforts were effective for urban minority youth. Furthermore, this study supports the idea that effective prevention programs need to teach students a variety of cognitive-behavioral skills to enhance assertiveness, resist advertisings, manage anxiety, communicate effectively, and develop strong interpersonal skills.

Botvin GJ, Griffin KW, Diaz T, Miller N, Ifill-Williams M: Smoking initiation and escalation in early adolescent girls: one-year follow-up of a school-based prevention intervention for minority youth . Journal of American Medical Womens Association, 54(3):139-44. 1999.

New Approaches to Preventing Drug Abuse

Background: Research has taught us much about what works and what does not work in preventing drug abuse. We have also learned that the most vulnerable times for initiating drug use are during transition periods. Transitioning from elementary school to middle school or junior high, for example, is a particularly challenging time for most youth. It is important that prevention planners develop programs that provide support during these highest-risk periods. Prevention programs that bring together a variety of audiences, such as those that are tailored to both parents and schools are showing some positive results. The Adolescents Transitions Program is one example of a school-based program that focuses on parenting practices and integrates interventions that are universal (geared to the general population), selective (targeted to groups at risk), and indicated (designed for individuals).

Advance: This paper presents a body of emerging research that is identifying and testing the necessary components to make a middle school prevention program successful. Building on past prevention research accomplishments, scientists are developing, modifying, and evaluating the family-based school intervention, Adolescents Transitions Program, particularly for students making the transition from middle school to junior high. The research confirms that the school setting is an effective place to engage families in promoting drug prevention activities. The process and rationale for implementing universal, selected, and indicated interventions is outlined in this paper. For example, researchers found that effective universal interventions include home visits to enhance participation and parent self-assessment (videotaping) which helps parents understand how their interactions with their child may be a risk factor for drug use. To reach high-risk youngsters and their families, a family-centered intervention that uses a multilevel strategy appears to maximize effectiveness.

Implications: The school setting has been shown to be an effective place to engage families in promoting prevention. This study addresses the design and implementation of effective family interventions within a school context and suggests that the integration of universal, selective, and indicated interventions may contribute significantly to reducing problem behavior and substance abuse.

Dishion TJ, Kavanaugh K: A multi-level approach to family-centered prevention in schools: process and outcome. Addictive Behaviors, 25:899-911. 2000.

Programs Can Bring About Positive Behavior Changes Among Youth Living with HIV

Background: There are an estimated 110,000 youth living with HIV (YLH) in the United States. Based on data from HIV seropositive adults, it is thought that a great majority of YLH continue their risky behaviors even after learning their serostatus. Therefore researchers believe it is important to develop prevention interventions that can curtail health behaviors that put individuals and their partners at additional risk. By combining two programs that have shown promising results for facilitating positive health behaviors, researchers have designed and evaluated a new prevention intervention geared toward YLH.

Advance: Prevention programs can effectively reduce risk acts among youth who have HIV. YLH aged 13 to 24 years were recruited from adolescent clinical care centers in four AIDS epicenters (New York, Los Angeles, San Francisco, and Miami). The youths were put into small groups that participated in two module interventions led by trained facilitators. Females assessed after completion of the first module, Stay Healthy, were found to have increased their number of positive lifestyle choices and increased their active coping skills when compared to those who did not receive the intervention. Social support coping also increased significantly among males and females after participating in this program. Assessments conducted after the second 11-session intervention, found that youths who participated in the intervention reported 82% fewer unprotected sexual acts, 45% fewer sexual partners, 50% fewer HIV-negative sexual partners, and 31% less substance use than those who did not receive any interventions.

Implications: Given that youth represent about 50% of all HIV infections worldwide and 18% of reported HIV cases in the United States, it is important that we have prevention interventions that can allow them to make the healthiest lifestyle choices possible for themselves and their loved ones. YLH who do not change their sexual risk acts or injection drug abuse may both infect others and become reinfected with new viral strains.

Rotheram-Borus MJ, Lee MB, Murphy DA, et al: Efficacy of a preventive intervention for youth living with HIV. American Journal of Public Health, March, 2001.

Understanding Critical Gender and Ethnic Differences in Pathways to Drug Abuse Improves Prevention Efforts

Background: Most prevention programs that have been researched and found to be effective focus on teaching individuals how to resist drug offers. What researchers haven't known is whether the skills that are being taught to individuals are suitable to their particular situation. For example, should the refusal skills being taught to female African American students be the same as what is being taught to European American boys? Fortunately, there is an emerging body of research that is beginning to focus on the role that ethnicity and gender play in adolescent drug use and refusals of drug offers. This information will help researchers develop prevention programs that are most suitable to the needs of a particular community.

Advance: While there are similarities across all youth, ethnicity and gender were found to play significant roles in both drug use and how and when an individual was offered drugs. Over 2,500 African American, Mexican American, and European American seventh grade students in Arizona were represented in this study that measured the relationship of ethnicity, gender, drug use, and resistance to drug offers. The study builds on earlier research by this group to provide a more in depth understanding of how these young people encounter and respond to drugs in the real world. The findings showed that Mexican Americans received more offers, used more drugs, and were more likely to be offered drugs by peer family members and at parties. European Americans were more likely to receive drug offers from acquaintances, at friends' homes, and on the street. African Americans were more likely to receive drug offers from dating partners and parents, in the park, and were more likely to resist offers of drugs by using explanations. Gender significantly affected drug offers and types of offers. It was also noted that across all groups there was limited knowledge of how to resist drug offers.

Implications: Having the skills to resist drugs is critical to the prevention of initial drug use. Knowing the situations in which drug offers typically occur among various groups can help better prepare individuals how to refuse those offers. Re-designing drug prevention skills to address differences in terms of gender, ethnicity, and circumstances can be an important contribution to improving drug abuse prevention intervention efforts.

Moon DG, Hecht ML, Jackson KM, Spellers RE: Ethnic and gender differences and similarities in adolescent drug use and refusals of drug offers. Substance Use and Misuse, 34(8):1059-83. 1999.

Smoking During Pregnancy May Increase the Risk of Behavioral Problems in Children

Background: Because maternal smoking during pregnancy has been associated with children's cognitive ability and language skills, it is speculated that it may also be related to children's negative behaviors such as impulsivity, attentional behavior, and hyperactivity. Confounding by variables such as demographics, maternal interpersonal distress, parenting factors, and other risk factors may however account for the relationship. Researchers are now attempting to disentangle the connection between maternal smoking and a child's negative behavior and confounding variables.

Advance: Researchers found a relationship between smoking during pregnancy and behavioral problems in toddlers while studying 2-year-olds of mothers who either smoked or did not smoke during pregnancy. This relationship was seen even after controlling for a number of psychosocial risk factors that have previously been shown to be associated with toddler's negative behaviors. In addition to maternal smoking, two other risk factors involving discipline and conflict in the mother-child relationship were identified. Three possible causes by which smoking may influence childhood behavioral problems were suggested: 1) smoking may narrow placental blood vessels affecting fetal nutrition and leading to problems with fetal brain development; 2) stressed mothers may tend to smoke and the stress itself may effect fetal brain development; 3) smoking affects the infant's health (e.g. low birth weight) which, in turn, affects the child's behavior when a toddler.

Implications: The findings suggest that maternal smoking during pregnancy has an adverse effect on a child's behavior. Approximately 800,000 children are born each year to women who smoke. The physical risks of maternal smoking for mother and child, such as lung cancer and low birth weight, respectively, are serious. Additionally, research now suggests that maternal smoking may have long-term negative effects on children's behavior, thus potentially overburdening school systems and other facilities that need to attend to these behavioral problems.

Brook JS, Brook DW, Whiteman M: The influence of maternal smoking during pregnancy on the toddler's negativity. Archives of Pediatric Medicine, 154(4):381-5. 2000.

A New Product That May Prevent HIV Transmission Enters Clinical Trials

Background: Heterosexual transmission is a primary mode of spreading HIV, especially in women. While currently used spermicides, such as nonoxynol-9 (N-9), rapidly inactivate HIV in a test-tube, results from recently completed clinical trials fail to support the test-tube observations. In addition, clinical information suggests that frequent use of a N-9 formulation may even *facilitate* sexual transmission of HIV. Now, investigators are trying to develop new topical products that can block the entry of the HIV virus without causing excessive irritation to the lining of the vagina and cervix.

Advance: NIH-supported researchers recently received a patent on a new microbicide based on extracts from seaweed called "carrageenans." The product, termed PC-515, acts directly in the vagina to block entry of the HIV virus. In addition, the effect of the product is long-lasting: researchers have observed that the activity of PC-515 lasts more than 24 hours in animal models. PC-515 has proceeded to phase II clinical trials in South Africa and Thailand, which will involve around 300 women and will provide additional information on the safety of the product. A manufacturing process has been developed to produce large quantities of the material, and a very affordable applicator for the product has already been selected.

Implications: With females accounting for a growing share of new AIDS cases, both nationally and internationally, topical microbicides are urgently needed to protect women from becoming infected with HIV after intercourse. This situation is particularly critical since studies have shown that N-9 spermicides do not appear to protect women from infection. The PC-515 formula is in advanced stages of safety evaluation and should undergo efficacy testing within a year or two. If the results from pre-clinical, animal model studies can be confirmed in clinical trials, this new product will represent a major advance in our ability to limit the spread of HIV.

Johansson EDB, Maguire RA, Phillips DM: Pushing the frontier of science - the population council's microbicide basic science network on vaginal microbicide research. International Journal of Gynecology and Obstetrics, 67 (Supplement 2):S117-24. 1999.

Mathematical Model May Help Reduce Antibiotic Resistance

Background: Despite careful sanitation practices put in place to keep hospitals clean, microorganisms thrive due to the concentration of sick patients. In hospitals, normally harmless bacteria can cause disease when they are passed between patients with weakened immune systems – either because the patients are in close proximity or due to the fact that patients share health care providers. These bacteria can then multiply out of control in normally sterile environments such as the bloodstream or airways. Especially worrisome are microbial populations resistant to important antibiotic medicines. To stem the spread of antibiotic-resistant bacteria in hospitals, many strategies have been tried, including improved hygiene, limiting the use of antibiotics for which resistance is high, and cycling between different drugs. In most cases the causes of antibiotic resistance and the effectiveness of various treatments have not been formally tested. A deeper understanding of these processes is critically needed.

Advance: Using mathematical modeling techniques, a team of biologists has come up with a way to gauge the effectiveness of the various methods hospitals now use to control antibiotic resistance. The scientists' new model came up with a few surprising predictions. The first was that hand washing and other efforts to reduce the spread of bacteria between hospital patients should have a greater impact on antibiotic-resistant strains of bacteria than on drug-sensitive strains. Another important prediction made by the model was that researchers should be able see the effects of a successful intervention on a time scale of weeks to months. This is considerably faster than the years or even decades scientists anticipate it takes resistance control measures to work in open communities. The model also predicted, unexpectedly, that hospital staff can reduce the number of bacteria resistant to certain antibiotics by substituting the use of other antibiotic drugs that haven't yet spawned resistant bacteria.

Implications: The results of this study provide hope in the otherwise gloomy scenario of antibiotic resistance, an important health threat in hospitals. The mathematically based model may help future researchers better tailor studies to evaluate antibiotic resistance prevention methods and pinpoint methods that work. For instance, based on the model's predictions the authors suggest that studies should be designed to look for rapid changes in the prevalence of bacteria in hospitals in response to efforts to control resistance. If antibiotic resistance persists beyond several weeks, hospital staff should suspect a hidden reservoir of resistant bacteria, such as contaminated work surfaces or medical instruments. [secondary – tools]

Lipsitch M, Bergstrom CT, Levin BR: The epidemiology of antibiotic resistance in hospitals: paradoxes and predictions. Proceedings of the National Academy of Sciences, 97(4):1938-43. 2000.

Study Sheds New Light on Genetic Predisposition to Obesity

Background: The discovery of the role of leptin and the leptin receptor in the regulation of food intake and energy expenditure provided promise for better understanding and control of body fat accumulation and obesity. However, while leptin therapy has prevented obesity in rats and mice, it has had mixed results in humans. Further study has shown that the genetic basis for leptin and other hormones related to obesity is more complex than first thought.

Advance: A study was undertaken to examine the effects of several leptin and leptin receptor gene variants on measures of body composition related to obesity. A variant in the leptin receptor gene, called QR223, was found to be associated with higher fat levels in middle-aged white males, suggesting that their resulting leptin receptor is defective in recognizing when ample body fat stores exist, thus leading to excess fat accumulation. Although the QR223 variant was also found among women and blacks in the study, it was not associated with fat levels in these groups.

Implications: This finding suggests that leptin therapy might have better effects if targeted to middle-aged white men who have the QR223 leptin receptor variant. The lack of association between QR223 and fat levels in women and blacks suggests that other hormonal or genetic factors are likely to interact with QR223. Understanding those factors will be an important step in developing effective preventive and therapeutic strategies.

Chagon YC, Wilmore JH, Borecki IB, et al: Associations between the leptin receptor gene and adiposity in middle-aged caucasian males from the heritage family study. The Journal of Clinical Endocrinology & Metabolism, 85(1):29-34. 2000.

Molecular Snapshot of Pain and Inflammation Initiation

Background: Pain, inflammation, and even cancer are human conditions for which new therapeutic agents could be developed based on recent structural discoveries made by a group of scientists. These scientists determined the three-dimensional structure of a critical enzyme, cyclooxygenase-2, as it bound to its substrate, arachidonic acid.

The key lies with a group of hormone-like substances called prostaglandins. These are the compounds that contribute to pain and inflammation; many common pain killers such as aspirin act by inhibiting prostaglandin production. Initiation of prostaglandin production begins with the binding of an enzyme, cyclooxygenase-2 (COX-2) with arachidonic acid. Blocking this reaction could potentially reduce pain and inflammation by preventing prostaglandin development. There might also be a connection between COX-2 and cancer because it has been observed that elevated levels of COX-2 are linked to tumor growth. In fact, tumor growth in the laboratory can be block with agents that block COX-2's action.

Advance: These scientists, using X-ray crystallography techniques, were able to "photograph" the molecular structure of COX-2 just as it was binding to its substrate, arachidonic acid. The "snapshot" also caught the initial product of the reaction, prostaglandin G2, still bound to the enzyme in exactly the same way scientists predicted from earlier experiments.

Implications: Many people who use pain killers experience stomach upset. This is because there are two forms of cyclooxygenase – COX-1 that is present in the stomach and whose products protect the stomach lining from irritation and COX-2 whose products result in pain and inflammation. Aspirin and similar drugs target both enzymes, resulting in pain relief but at the cost of stomach upset and possible ulcers. By capitalizing on these recent findings, drug companies can better tailor therapeutics that block COX-2, but leave COX-1 alone. These new drugs, then, would provide pain relief without stomach upset.

Kiefer JR, Pawlitz JL, Moreland KT, et al: Structural insights into the stereochemistry of the cyclooxygenase reaction. Nature, 405(6782):97-101. 2000.

Role of Diet and Genetic Mutation in Preventing Lung Cancer

Background: It has long been noted that diets high in vegetables reduce cancer risks in people. Of particular benefit are the cruciferous vegetables such as broccoli, cauliflower, cabbage, watercress, bok choy, and others. These vegetables are high in precursors of an important class of anticancer agents, the isothiocyanates (ITC). A recent study has shown an important gene-environment interaction that influences the benefit of ITC in reducing cancer risks.

Advance: Everyone has metabolizing enzymes that are responsible for breaking down and eliminating the different compounds to which we are exposed. These compounds would include beneficial substances such as ITC and harmful substances such as tobacco carcinogens. One such enzyme is GSTM1. It is thought that people who lack this enzyme are at increased risk of lung cancer because they are unable to inactivate carcinogens and, thus, would have a higher exposure than people with active GSTM1 who would quickly excrete cancer-causing substances.

But researchers have recently shown that having active GSTM1 can also be a risk factor in certain circumstances. That is because this enzyme also breaks down and eliminates beneficial dietary ITC. Thus, people with high levels of GSTM1 would have lower levels of the critical ITC anticarcinogen, a condition that could increase their cancer risk.

A unique aspect of this study is that the researchers used a marker they had previously developed for ITC so that levels could be assayed in urine. Questionnaire assessment of ITC requires detail on many dietary items not included in many frequency questionnaires. In this study 18,244 men in China were evaluated. Those with detectable levels of ITC had a 40% decrease in lung cancer risk. Of those lacking the ITC-eliminating enzyme, GSTM1, the lung cancer risk was reduced 64%.

Implications: Understanding how diet and underlying genetic susceptibilities interact to reduce disease risk is vital in helping people improve their health. This study demonstrates a key component of the complex gene-environment interactions that control our health. It also represents the first time that a biologic marker for ITC consumption has been used to assess reductions in cancer risks. These more refined methods over traditional reliance on patient recall will greatly improve our understanding of the true impact of diet in improving health.

London SJ, Yuan JM, Chung FL,et al: Isothiocyanates, glutathione S-transferase M1 and T1 polymorphisms, and lung cancer risk: a prospective study of men in Shanghai, China. The Lancet, 356(9231):724-9. 2000.

From Mother to Daughter to Grandson - The Legacy of DES

Background: Once used by pregnant women to prevent miscarriage, the potent synthetic estrogen, diethylstilbestrol (DES), was shown to cause health problems in women exposed to DES *in utero* ("DES daughters"). These women were at risk of developing a rare vaginal cancer, clear cell adenocarcinoma, as well as having reproductive abnormalities. To date, DES sons have shown increased reproductive tract abnormalities, but not an increased cancer risk although this is a possibility as the population ages.

Scientists developed a mouse model that mimicked human effects from this drug. The two-year life span of the mouse enables researchers to generate results quickly and to use these results as a guide for how to monitor DES daughters. For example, early results in mice showed an increase in ovarian cysts, a finding that was verified in follow-up studies in DES daughters. More recently, mouse studies have also shown that adverse effects of DES exposure can show up in DES granddaughters, even though this group had no known direct exposure to DES. In a multigenerational mouse study, it was shown that those that were DES granddaughters had a much higher cancer susceptibility than controls. Reproductive effects, however, were not transmitted across generations. These findings will have important public health consequences, giving an early warning to physicians and health officials that they need to monitor DES granddaughters as carefully as DES daughters in order to improve their chances of a healthy life.

New results in mice now show that "DES grandsons" are also affected. Third generation mice, although never exposed to DES, had reproductive tract tumors. Like the granddaughters, their fertility was not affected.

Advance: In this three-generation study, pregnant mice were exposed to DES. Their female offspring, upon maturity, were bred to untreated males. The third generation, which had never been exposed to DES, were bred upon maturity. The DES grandsons had the same fertility as control mice, but developed tumors in the testis and reproductive tract.

Implications: This study shows the unexpected – that the environmental exposures of one's parents and grandparents can have adverse effects on our own health, even if we have never been directly exposed to a particular compound. Although this multigenerational effect has only been demonstrated with DES, it suggests new avenues of investigation for assessing the many "environmental estrogens" that have been developed. Although these compounds have a far weaker estrogenic effect than DES, the possibility exists that subtle adverse effects could show up in our sons, daughters, grandsons, and granddaughters.

More immediately, this research proves that the sons of DES daughters need to be closely monitored by their physicians.

Newbold RR, Hanson RB, Jefferson WN, et al: Proliferative lesions and reproductive tract tumors in male descendants of mice exposed developmentally to diethylstilbestrol. Carcinogenesis, 21(7):1355-63. 2000.

Effects of Dioxin on Gender Ratios in Offspring of Exposed Men

Background: 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is considered to be one of, if not the most toxic man-made substance. It causes cancer and disrupts multiple hormonal functions. TCDD is a by-product of several manufacturing processes such as paper production and pesticide formulation.

On July 10, 1976, an explosion occurred at an herbicide manufacturing facility in Seveso, Italy. Approximately 30 kg of dioxin was released into the environment. It contaminated the soil of the surrounding area and many people were exposed. Many of these people have been followed for adverse health effects following the accident.

Advance: This paper reports a follow-up study on previous work that demonstrated a significant increase in the number of female births after the accident. Serum samples taken at the time of the accident were analyzed for TCDD. The data indicate a positive correlation between increased probability of female births with increasing TCDD concentration in the sera of the fathers. The effect starts at concentrations less than 20 ng/kg bodyweight – a level about 20 times higher than the normal TCDD concentration in people. This level of contamination is similar to doses that cause epididymal impairments in rats.

Implications: Dioxin is a ubiquitous toxin in that all human beings have some exposure. The Seveso incident occurred over 20 years ago and the effects on offspring gender ratios are still present. This fact demonstrates the persistence of dioxin and its adverse effects following exposure. Also, the level of exposure compared to "unexposed" populations is relatively low, suggesting that these effects may also be seen in the general population or susceptible individuals. These observations could have profound public-health implications.

Mocarelli P, Gerthoux PM, Ferrari E, et al: Paternal concentrations of dioxin and sex ratio of offspring. The Lancet, 355(9218):1858-63. 2000.

How Lead Exposure May Work to Damage the Developing Brain

Background: Elemental lead has been a bane to the existence of man since the beginning of time. Lead has been found in bones as old as 8,500 years. In the twentieth century, tetraethyl lead, used as a "no-knock" additive in automobile fuels, distributed lead to every corner of the world through car exhausts. Although leaded gasoline has been removed from the marketplace, and despite the fact that mean blood lead levels have been decreasing dramatically over the last two decades, lead poisoning remains a major public health problem, especially common in poor urban children. Relatively low-level lead exposure in children can cause permanent deficits in intelligence; however, the biologic mechanism for this effect is unknown.

Advance: Using a rodent model, a scientists showed that the effect of lead exposure on a child's brain may be due to reductions in growth and development of the brain's cortex. In rats, individual rodent whiskers are linked to sets of specific cells, known as barrel fields, in the sensory portion of the cortex. Scientists looked at lead-induced damage to the nerve cells that process sensory signals from the rat's whiskers.

Female rats who had just delivered pups were administered lead in their drinking water. The timing of the lead treatment coincided with the development of specific brain structures in the rat pups, which obtained the lead from nursing, and produced blood lead levels in the pups in the same range observed in many inner-city children. Lead exposure caused a decrease in the size of the structures – the "barrel fields"– in the rat pups' brains. This finding supports the hypothesis that lead exposure, at levels found in inner-city children, may impair the development of neural cortex and thus cause decreases in intelligence.

Implications: This study demonstrates that a dose-related decrease in the size of specific brain structures is observed in these rats after exposure to relatively low doses of lead during a critical developmental stage. These structural alterations occur in the animals, not at the elevated test doses used in other studies, but at doses equivalent to those actually seen in many poor inner-city children.

Wilson MA, Johnston MV, Goldstein GW, Blue ME: Neonatal lead exposure impairs development of rodent barrel field cortex. Proceedings of the National Academy of Sciences, 97(10):5540-45. 2000.

Urinary Tract Infections: Identification of Molecular Mechanisms of Infection

Background: Acute urinary tract infections (UTIs) are among the most common infectious diseases acquired by humans. UTIs account for over seven million visits to doctors' offices, and $1 billion in health care costs, annually. The bacterium *Escherichia coli* (*E. coli*) is the primary causative agent of UTIs. Among the earliest events in these infections are the molecular interactions that occur between the infecting organism (the pathogen) and the host cells (bladder cells). Colonization of host tissues by pathogenic (disease-causing) bacteria is usually mediated by substances called adhesins, which are found on the surface of the infecting microbe. The adhesins are responsible for recognizing and binding to specific receptor moieties of host cells. In many organisms, the adhesins are assembled into hair-like appendages called pili that extend out from the bacterial surface. In mice, it has been shown that a particular adhesin, called FimH, is required for pathogenic *E. coli* colonization. FimH must be complexed with another molecule, called a chaperone protein, for correct protein folding and expression. The pili on *E. coli* having FimH are designated "type 1" pili. In culture, antibodies to FimH, i.e., "vaccination," can prevent *E. coli* attachment to bladder cells.

Advance: Several scientific reports in the last year advanced knowledge of the molecular mechanisms of urinary tract infections. Extending previous studies using mice and cell culture, investigators found that monkeys vaccinated with FimH produced antibodies to it, and did not develop infections when challenged, suggesting that the FimH vaccine induced protective immunity. A second study found that FimH not only is critical for adherence of *E. coli* to bladder cells, but also for the actual invasion of the bacteria into the cells. It appears that FimH binding begins a cascade of events in the host cell membrane that results in internalization of the bacterium. A third study showed that the FimH chaperone protein is necessary for proper folding – and therefore function – of the FimH protein itself, but that a small amino acid segment of the chaperone could perform the folding function of the full chaperone. A fourth study examined pathogenic *E. coli* infection, involving FimH, in bone marrow-derived mast cells. Mast cell uptake of pathogenic *E. coli* was dependent on specialized invaginated areas of the cell called caveolae (meaning "little caves"), which contain a unique type of protein. The type 1 pili of *E. coli* with FimH attach to multiple caveolae on the mast cell, forming massive caveolae-like vesicles that internalize the bacteria. Compounds that disrupt caveolae block mast-cell bacterial uptake. This series of experiments strengthens the view that caveolae are centers from which multiple cellular signaling pathways originate. In the mast cells, they appear to be highly dynamic elements that can receive and transmit signals to activate internalization of bacteria.

Implications: These studies provide insights into the molecular mechanisms of pathogenic *E. coli* infection – and specifically host-parasite interactions – that will be critical in developing effective, long-lasting therapies and preventive strategies for UTIs. While research on FimH vaccines is in the early stages of development, it is moving closer to human trials. More detailed knowledge of the infectious process provides a number of potential targets for therapeutic and preventive approaches. Beyond providing a system in which to study molecular aspects of bacterial internalization, the mast cell

is of interest because it affords an opportunity to examine more closely how disease-causing bacteria manage to survive, and thrive, after being engulfed by the cell, knowledge which may itself offer eventual targets for prevention and therapy.

Langermann S, Mollby R, Burlein JE, et al: Vaccination with FimH adhesin protects cynomolgus monkeys from colonization and infection by uropathogenic *Escherichia coli*. The Journal of Infectious Diseases, 181(2):774-8. 2000.

Martinez JJ, Mulvey MA, Schilling JD, Pinkner JS, Hultgren SJ: Type 1 pilus-mediated bacterial invasion of bladder epithelial cells. The European Molecular Biology Organization, 19(12):2803-12. 2000.

Barnhart MM, Pinkner JS, Soto GE, et al: PapD-like chaperones provide the missing information for folding of pilin proteins. Proceedings of the National Academy of Sciences, 97(14):7709-14. 2000.

Shin JS, Gao Z, Abraham SN: Involvement of cellular caveolae in bacterial entry into mast cells. Science, 289(5480):785-8. 2000.

Mechanisms of Chromosome Missegregation in Cancer Cells

Background: When a normal, healthy cell begins to divide, its chromosomes line up along the center of a structure called a spindle. Long thread-like fibers called microtubules attach each chromosome to the ends opposite the spindle, or the spindle poles. As the cell divides, the microtubules guide the chromosomes to form two new cells. In cancer cells this delicate process becomes faulty, resulting in a large number of chromosome deletions, translocations, and structural abnormalities. Indeed, abnormal nuclear morphology is one of the key features used by pathologists to diagnose cancer.

Advance: Researchers at the University of Pittsburgh have provided the first graphic illustration of a mechanism by which chromosome segregation can go awry in cancer cell division, leading to genetic defects such as abnormal or missing chromosomes. Using fluorescent markers to label chromosomes and cell structures involved in the division of oral cancer cells, the researchers have captured, through fluorescence microscopy, the mechanisms by which chromosomes are distributed unevenly during cancer cell division. This is the first study to show how multiple spindles form, how the nuclear mitotic apparatus protein may be involved, and why cancer cells contain too few or too many chromosomes. They also showed how chromosomes in cancer cells often break and reform, producing chromosomes with extra sections that may contain abnormal numbers of genes. This process, called a breakage-fusion-bridge cycle, is repeated with each cell division, yielding chromosomes with ever-increasing copies of genetic material. These amplified segments may contain multiple copies of genes that drive cancer cell growth.

Implications: Smoking damages chromosomes that somehow leads to micronuclei and chromosome breaks. This study shows how these events may occur in oral cancer cells. By understanding this process, it may be possible to intervene and prevent genetic changes that contribute to cancer growth. Using this information, investigators may also be able to screen individuals at risk for cancer, as well as develop and apply better prevention and treatment strategies.

Saunders WS, Shuster M, Huang X, et al: Chromosome instability and cytoskeletal defects in oral cancer cells. Proceedings of the National Academy of Sciences, 97(1):303-8. 2000.

Advanced Imaging Technique Helps Predict Risk for Alzheimer's Disease

Background: Each year Alzheimer's disease (AD) and other dementias cast a shadow over a growing number of lives. An estimated 4 million Americans now suffer from AD, while countless others are impaired by related dementia disorders. Early detection of AD is difficult because preclinical symptoms such as mild memory loss may be overlooked as a common and expected condition among the elderly. Improved diagnostic techniques are needed, since existing tools have limited ability to predict which individuals with mild memory loss will progress to AD.

Advance: Investigators at the NIH-supported Neuroimaging Analysis Center have developed advanced imaging techniques that can identify distinctive brain changes that presage AD. The investigators used magnetic resonance imaging (MRI) to determine whether persons in the preclinical phase of AD could be accurately identified before they developed clinically diagnosed dementia. The MRI scans of various brain regions showed significant differences between normal individuals and those who later developed AD and predicted which patients with memory impairment would develop AD.

A second study conducted at the NIH-supported Center for Advanced Magnetic Resonance Technology at Stanford University showed that magnetic resonance spectroscopy may be a suitable noninvasive tool for monitoring disease progression in patients with AD. Serial measurements of the brain chemical N-acetyl aspartate, which is a marker for living brain cells, showed significant reductions in patients with AD over a 1-year period. This work is particularly important in that it may enhance evaluation of the many new drugs currently being developed to treat AD.

In a third study, investigators have found that the patterns of brain activation during tasks requiring memory differ depending on the genetic risk of AD and may predict a subsequent decline in memory.

Implications: Magnetic resonance imaging provides the opportunity to detect AD at an early stage. Such a diagnosis is important because of the arrival of drugs that treat the symptoms of Alzheimer's disease and drugs that may delay progression of the disease. [secondary – diagnosis]

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Bookheimer SY, Magdalena H, Strovjwas BS, et al: Patterns of brain activation in people at risk for alzheimer's disease. The New England Journal of Medicine, 343(7):450-5. 2000.

Early Expression of Anti-insulin Autoantibodies of Humans and the NOD Mouse: Evidence for Early Determination of Subsequent Diabetes

Background: Type 1 diabetes strikes approximately 1 in 300 children and is one of the most frequent chronic life-threatening illnesses of children. Scientists have long known that development of anti-insulin autoantibodies (immune substances directed against one's own body) can precede the clinical development of diabetes, but have not known how early these antibodies can be detected.

Advance: To correlate development of disease with the presence of autoantibodies, researchers developed a sensitive assay for anti-insulin autoantibodies. The technique will permit public health screening for diabetes risk whenever effective preventive therapies become available. The investigators discovered that children developed anti-insulin autoantibodies in the first year of life, and 4 of 5 children expressing such antibodies progressed to diabetes before they were 3.5 years old. Of 929 children not expressing antibodies, only 1 has progressed to diabetes, and that child developed anti-insulin autoantibodies at a second visit at 1.1 year of age. In addition, the investigators found that a diabetic mouse model of childhood diabetes expressed similar antibodies at an early age, which will facilitate studies of diabetes prevention. With knowledge that autoimmunity occurs very early, the investigators suggest that immunologic therapies for preventing childhood diabetes should be tested in children before they develop autoantibodies.

Implications: There is an international effort to develop effective therapies for preventing diabetes. Assays like the one described in this study will form the basis for screening when such therapies are tested and proven effective. [secondary – diagnosis]

Yu L, Robles DT, Abiru N, et al: Early expression of antiinsulin autoantibodies of humans and the NOD mouse: evidence for early determination of subsequent diabetes. Proceedings of the National Academy of Sciences, 97(4):1701-6. 2000.

Daily Smoking Not Necessary for Nicotine Dependence in Young People

Background: More than 3 million adolescents in the United States smoke, and every day another 6,000 young people begin smoking. While cigarette smoking has been declining among American adults, the number of adolescents who smoke has risen sharply since 1992. Not only are more young people smoking, but they are taking up the habit at a younger age. Studies show that the earlier people start to smoke, the more cigarettes per day they will smoke as adults and the more serious the health problems they will develop in later life as a result of tobacco use. Like adult smokers, adolescents report frequent unsuccessful attempts to quit, and they cite withdrawal symptoms and the "urge to smoke" among the reasons why they find it difficult to give up smoking. However, because many young people have not yet become daily smokers, researchers have tended not to regard them as nicotine dependent. The traditional model for the development of nicotine dependence is progression from experimental tobacco use to occasional use, then to daily use that increases in frequency, resulting in dependence – a process that can take months or years.

Advance: Recently, researchers have found evidence of nicotine dependence and withdrawal among young tobacco smokers *before* they become daily smokers. NIH-supported researchers found that 63% of 7th-grade students (ages 12-13) who smoked one or more cigarettes a month reported experiencing one or more symptoms of nicotine dependence. These symptoms included cravings, withdrawal symptoms (depressed mood, irritability, anger, anxiety, difficulty concentrating, and restlessness) and loss of control over the amount and duration of tobacco use. More than one in five of these students reported symptoms of nicotine dependence within four weeks of beginning to smoke one or more times a month. Another group of researchers reviewed the literature on nicotine dependence and withdrawal in young smokers. They found that, compared with adult smokers, adolescents were less likely to smoke daily or regularly, and those who smoked daily smoked fewer cigarettes. Nevertheless, 20-68% of adolescent smokers were classified as dependent, and 66% or more reported experiencing withdrawal symptoms when they cut down or tried to quit smoking.

Implications: These studies reveal that, contrary to past assumptions, adolescents who have never smoked daily may encounter significant difficulty in trying to give up smoking. This discovery has important implications for public health and future research, revealing the need to develop new assessment instruments for studying tobacco use in young people. These research findings also point to the importance of developing new strategies to prevent young people from starting to smoke and to intervene early to help young smokers quit.

Colby SM, Tiffany ST, Shiffman S, Niaura RS: Are adolescent smokers dependent on nicotine? A review of the evidence. Drug and Alcohol Dependence, 59(Supplement 1):S83-95. 2000.

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DiFranza JR, Rigotti N, McNeill AD, et al: Initial symptoms of nicotine dependence in adolescents. Tobacco Control, 9(3):313-9. 2000.

Noise Induced Hearing Loss

Background: The search for a safe and reliable pre-exposure index of vulnerability to acoustic injury has been an important, but difficult, primary research question in noise-induced hearing loss (NIHL) due to the tremendous inter-subject variability seen among individuals with similar noise exposures. By knowing who is at risk to NIHL, focused and effective preventive measures can be developed and targeted to those individuals most at risk.

Advance: An investigator has recently developed a procedure in an animal model to screen for risk of NIHL. This procedure is simple and nontraumatic, and involves the measurement of a neuronal feedback pathway to the inner ear. The feedback pathway is thought to protect the ear from acoustic injury, and intersubject differences in the feedback pathway appear to underlie the differences in vulnerability to NIHL. The application of this procedure to human populations is a logical and very exciting next step.

Implications: To accelerate research progress on NIHL, the NIH convened a workshop in December 1998 on "Research Opportunities in the Biology of Noise- Induced Hearing Loss". The research workshop focused on cutting-edge research in cell and molecular biology and genetics that impact on the biology of NIHL. A Request for Applications for exploratory/developmental grants on the "Biological Mechanisms of Noise Induced Hearing Loss" was published in the NIH Guide to Grants and Contracts on May 30, 2000. Applications are being solicited in the area of NIHL, including a) cell injury, cell death and cell survival, b) susceptibility to NIHL with a focus on environmental and genetic factors, and c) protection and rescue from NIHL from a biological/pharmacological perspective. Applications are due September 21, 2000, and up to seven applications are expected to be awarded in this important research area.

Maison SF, Liberman MC: Predicting vulnerability to acoustic injury with a noninvasive assay of olivocochlear reflex strength. The Journal of Neuroscience, 20(12):4701-7. 2000.

Strong Genetic Component to Otitis Media

Background: Otitis media (middle ear infection) remains the most common reason for a sick child to consult a physician and is the most common reason that children receive antibiotics or undergo surgery. Previous anatomical, physiological and epidemiological data suggested that this common disease has a hereditary component.

Advance: NIH-supported investigators have studied twins and triplets to determine the extent to which genetic factors play a role in otitis media. Twin and triplet studies are a powerful method of determining the contribution of genetics to a disease, because the potentially confounding effect of environmental factors is significantly reduced with this study design. The results of the study, which utilized 175 sets of newborn twins and triplets, clearly indicate that there is a strong genetic component to the rate of occurrence of otitis media in children.

Implications: The implications of these findings for both immediate and future improvements in treatment of otitis media are numerous. In the short term, these findings will allow the primary care physician to identify the siblings and offspring of affected patients as high-risk cases. Such patients could be followed more closely for early detection and treatment, which may reduce or prevent developmental problems associated with this condition. In addition, the identification of the genetic factors mediating this effect could eventually result in DNA diagnostic tests to identify individuals at increased risk. Finally, studies of the mechanisms by which the responsible genes affect the frequency of otitis media could lead to new approaches for intervention and treatment. [secondary – treatment]

Casselbrant ML, Mandel EM, Fall PA, et al: The heritability of otitis media: A twin and triplet study. Journal of the American Medical Association, 282(22):2125-30. 1999.

Minor Variations in a Gene for a Bone Protein Lead to Lower Bone Density

Background: Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Currently there is no accurate measure of overall bone strength. Bone mineral density (BMD) is frequently used as a proxy measure for bone strength and does account for approximately 70 percent of bone strength. Approximately 500,000 elderly women in the United States are newly diagnosed with spinal fractures every year, as the strength of the spine, mainly determined by the density of the bone and its cross-sectional area, declines with age.

A recent report has associated low spinal bone mass and spinal fractures in older women with minor changes in a gene for collagen, the major protein in bone tissue. Major mutations (changes) in the collagen gene can lead to very disordered bone as in osteogenesis imperfecta, a disease manifesting in early life with multiple fractures and growth abnormalities. If minor variations in the collagen gene are associated with differences in bone density, these effects should be manifest in childhood.

Advance: Researchers studied 100 prepubertal girls. They measured BMD and assessed the bone size and genetic makeup of the collagen gene in each girl. They found that girls with a particular type of collagen gene variant had almost 50 percent lower BMD than girls with a different collagen gene variant, but that this gene had no effect on bone size. Thus, these minor variations in the gene for collagen protein, while not causing outright disease, may define a high susceptibility group for osteoporosis later in life.

Implications: Understanding and identifying genetic susceptibility to osteoporosis early in life may facilitate the targeting of interventions to those who will most profit from them.

Sainz J, van Tornourt JM, Sayre J, Kaufman F, Gilsanz V: Association of collagen type 1 a1 gene polymorphism with bone density in early childhood. The Journal of Clinical Endocrinology and Metabolism, 84(3):853-5. 1999.

Low Calcium Intakes and Absorption Contribute to Increased Fracture Risk in the Elderly

Background: Decreased calcium intakes are common among the elderly. The recommended level of 1200 mg of elemental calcium per day is challenging for many elderly people to consume. This is thought to be a factor in the elevated parathyroid hormone levels in the elderly and a contributor to bone loss and fractures. As people age, they become less able to absorb calcium from the food they have eaten. This could be a particular problem for people who already have low calcium intake. Failure to get enough calcium into the body can contribute to the weakening of the bones (osteoporosis) that happens as people age, especially women.

Advance: Researchers studied 5452 women 69 years of age or older who were participating in a large study of osteoporosis being conducted in four different areas of the United States. The researchers measured what fraction of a standardized amount of calcium each woman absorbed into her blood after swallowing a special calcium supplement. They then contacted the women every 4 months to learn whether they had suffered a fracture during that time. The researchers also checked medical records to confirm the occurrence and location of every fracture. The women were followed for about 5 years.

Seven hundred twenty-nine (13 percent) of the women suffered a fracture at a location other than the spine; 153 of these were fractures of the hip. After accounting for the effects of age, the researchers found that women who absorbed the smallest amounts of calcium were at increased risk for hip fracture. This association was most striking for women whose intake of calcium was low to begin with. Decreased calcium absorption was not associated with fractures at locations other than the hip.

Implications: Decreased calcium absorption can increase the chance of osteoporosis-related hip fractures in older women, especially when it occurs in women with low dietary calcium intake. This study suggests that it may be useful to find ways to improve calcium absorption, and emphasizes the importance of getting enough calcium in the diet.

Ensrud KE, Duong T, Cauley JA, et al: Low fractional calcium absorption increases the risk for hip fracture in women with low calcium intake. Annals of Internal Medicine, 132(5):345-53. 2000.

Gene Found for Papillon-Lefevre Syndrome – A Disorder Affecting Skin and Gums

Background: Papillon-Lefevre syndrome (PLS) is a rare but devastating condition that produces areas of thick, cracked skin and causes premature loss of all teeth by young adulthood. The rapid loss of both primary and permanent teeth mirrors the most severe forms of periodontal disease.

Advance: One study narrowed the location of the gene responsible for this disorder to a small region of chromosome 11. The second study identified a gene that codes for an enzyme called cathepsin C as the one which is responsible for PLS. Individuals with the disorder have mutations in this gene which are thought to inactivate the enzyme.

Implications: Identification of the gene for PLS should help in our understanding of the process by which periodontal disease attacks the general population and may lead to a test for periodontal disease susceptibility. It could also lead to gene therapy for those with PLS.

Hart TC, Hart PS, Bowden DW, et al: Mutations of the cathepsin C gene are responsible for papillon-lefevre syndrome. Journal of Medical Genetics, 36(12):881-7. 1999.

Toomes C, James J, Wood AJ, et al: Loss-of-function mutations in the cathepsin C gene result in periodontal disease and palmoplantar keratosis. Nature Genetics, 23(4):421-4. 1999.

Nasal Administration of Amyloid-ß Can Reduce Brain Amyloid-ß Deposition

Background: Recent studies using transgenic mice that carry mutant human forms of amyloid precursor protein and show extensive amyloid plaque formation with advancing age have shown that an amyloid vaccine causes an immune response in these mice and that this treatment almost eliminates amyloid plaques and associated neuropathology. Plaques may be cleared by activated scavenging microglia engulfing and destroying plaque amyloid. Research this year has shown encouraging results in the development and testing of the amyloid vaccine approach. For example, the vaccine is not toxic in a number of animal studies, including non-human primates.

Advance: A study by NIH-funded researchers provides a second approach to the antibody-mediated removal of amyloid plaques. Administration of the same amyloid as used in the vaccine but now by nasal spray also induces an immune response in the same transgenic mice. When young transgenic mice were given the human amyloid-ß spray, they had a much lower amyloid burden at middle age than animals that did not receive the spray vaccine. There was also a reduced brain immune tissue response. The reduction was not as dramatic as that reported for the vaccination response. However, these results open the door to an alternative approach for the treatment and prevention of Alzheimer's disease (AD) that may be better tolerated long-term than the injected amyloid vaccine.

Implications: This study suggests a novel and easily administered approach to reduction of amyloid plaque burden, and, a possible future preventive measure for Alzheimer's disease.

Weiner HL, Lemere CA, Maron R, et al: Nasal administration of amyloid ß peptide decreases cerebral amyloid burden in a mouse model of Alzheimer's disease. Annals of Neurology, 48(4):567-79. 2000.

Fitness Affects Mortality Risk Regardless of Fatness

Background: Obesity is associated with several chronic conditions and disease risk factors, including low cardiorespiratory fitness. Cardiorespiratory fitness is a measure of exercise capacity and is typically determined by measuring oxygen consumption as a person exercises as hard as possible on a treadmill. Both obesity and low fitness are related to risk for morbidity and mortality. It has been unclear to what degree obesity's relationship to mortality is due to its association with low fitness, or to what degree low fitness' relationship to mortality is due to its association with obesity.

Advance: Two recent studies sought to clarify the interrelationship between fitness, fatness, and all-cause or cardiovascular mortality. In the first study, investigators followed 21,925 men ranging in age from 30-83 years of age for an average of eight years. Men in the study were classified according to fatness, and classified as fit or unfit based on exercise testing. Within each category of body fatness, men classified as "fit" were at lower risk of death from both cardiovascular disease and all-cause mortality. In addition, among fit men, obesity was not significantly related to risk of death. In another study of 25,714 men conducted over 10 years, low fitness was associated with higher mortality in all weight groups. The strength of the effect of low fitness on mortality risk was approximately fivefold for cardiovascular disease, and about triple for all-cause mortality. These effects are in the same range as other strong risk factors such as diabetes and high cholesterol levels.

Implications: Though to date many interventions used to prevent and treat obesity-associated conditions have focused on weight-loss strategies, the present data indicate that equally, if not more, important benefits could be gained from strategies that improve cardiorespiratory fitness (especially in persons with low fitness) to reduce the risk of chronic diseases in overweight and obese individuals.

Lee CD, Blair SN, Jackson AS: Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. The American Journal of Clinical Nutrition, 69(3):373-80. 1999.

Wei M, Kampert JB, Barlow CE, et al: Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. The Journal of the American Medical Association, 282(16):1547-53. 1999.

Inadequate Treatment of Hypertension and Atrial Fibrillation in the Elderly

Background: According to a recent national survey, 60-70% of older Americans – those aged 60 years and older – have high blood pressure. Despite the considerable amount of scientific evidence that hypertension is an important risk factor for cardiovascular disease in all age groups, data suggest that less than 25% of persons over the age of 60 years have their blood pressure under control. Uncontrolled or inadequately controlled high blood pressure can lead to heart attack, stroke, heart failure, kidney disease, dementia, or blindness. In patients with atrial fibrillation (AF), a common heart rhythm abnormality in older persons that predisposes a person to circulating blood clots, warfarin, a drug used to inhibit blood clotting, dramatically reduces the risk for stroke. However, use among outpatients with AF has not been widely studied.

Advance: Two recent studies have suggested that older patients may be under-treated for both high blood pressure and AF. In the first study, investigators examined the relationship between blood pressure level achieved through anti-hypertensive drug therapy and incidence of heart attack. A higher blood pressure level despite drug treatment; i.e., "poor control, " was directly related to risk of heart attack. About 15.3% of the heart attacks could be explained by poor blood pressure control. In the second study, investigators assessed the rates and predictors of warfarin use in a large number of AF patients in an HMO. These were patients aged 65 to 74 years, with no reason to avoid warfarin, who had a history of previous stroke, high blood pressure, or both. Among such patients, only 55% received the drug. Even in a subset of ideal candidates for warfarin, only 62.1% received it.

Implications: The findings suggest that developing new strategies to improve blood pressure control in treated older hypertensive patients, especially in those patients with a small residual elevation in blood pressure, might prevent an estimated 15% of heart attacks in this population. Additional findings suggest that many apparently eligible patients with AF and at least one additional risk factor for stroke, especially high blood pressure, did not receive warfarin therapy. New interventions that improve the use of warfarin and anti-hypertensive treatment among appropriate candidates in usual, day-to-day, clinical care are needed.

Kaplan RC, Psaty BM, Heckbert SR, et al: Blood pressure level and incidence of myocardial infarction among patients treated for hypertension. American Journal of Public Health, 89(9):1414-7. 1999.

Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE: Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Annals of Internal Medicine, 131(12):927-34. 1999.

Identifying Gene Variants Affecting Disease Risk Factors and their Interactions with Exercise

Background: The increase in body fat and loss of muscle mass that occurs with advancing age can contribute substantially to many age-related diseases of older Americans, such as diabetes and cardiovascular disease. Intervention strategies such as dieting, alone or in combination with endurance and/or strength training, can be effective in preventing or improving these conditions. However, there can be large variances in people's responses to these interventions. Aside from differences in lifestyle choices, an individual's genetic background likely influences responses to behavior interventions, since obesity, muscle mass, and blood cholesterol levels are traits that can have large heritable components. Detection of specific genes affecting such factors provides a way of identifying individuals who are likely to respond favorably to a given type of intervention.

Advance: Three recently published studies have identified genes that could interact with environment to affect changes in cholesterol levels. One study examined the genetic influence on an enzyme, lipoprotein lipase (LPL), that affects levels of blood cholesterol. A specific variation in the LPL gene was associated with lower levels of total cholesterol and LDL-cholesterol (high LDL levels are associated with high risk for heart disease) in a group of overweight, postmenopausal women. Another study in older men found the same LPL gene variant to be associated with greater exercise-induced increases in HDL-cholesterol (a type of cholesterol thought to protect against heart disease). The third study suggests that variants of the gene for apolipoprotein E (APOE), previously shown to influence blood cholesterol levels, are related to exercise-induced increases in HDL-cholesterol concentrations in middle-aged and older, overweight men. One form (APOE2) was associated with greater exercise-induced increases in HDL, compared with APOE3 and APOE4.

Implications: These data taken collectively illustrate the potential value of identifying variations in specific genes that interact with environment and lifestyle interventions to affect risk factors (such as cholesterol), for chronic age-related diseases such as cardiovascular disease. In the long term, knowledge of the specific genes controlling these risk factors, and how their variants interact with exercise and diet, will allow the identification of individuals most likely to respond to particular interventions. Ultimately this will lead to the development of more targeted/ individualized strategies to reduce risks for chronic age-related diseases.

Nicklas BJ, Ferrell RE, RogusEM, et al: Lipoprotein lipase gene variation is associated with adipose tissue lipoprotein lipase activity, and lipoprotein lipid and glucose concentrations in overweight, postmenopausal women. Human Genetics, 106(4):420-4. 2000.

Hagberg JM, Ferrell RE, Dengel DR, Wilund KR: Exercise training-induced blood pressure and plasma lipid improvements in hypertensives may be genotype dependent. Hypertension, 34:18-23. 1999.

Hagberg JM, Ferrell RE, Katzel LI, Dengel DR, Sorkin JD, Goldberg AP: Apolipoprotein E genotype and exercise training-induced increases in plasma high-density lipoprotein (HDL)-and HDL_2-cholesterol levels in overweight men. Metabolism, 48(8):943-5. 1999.

Natural Killer Cell Activity and Resistance to Tumor Metastasis

Background: In spite of the many important advances in the study of pediatric cancer, critical questions remain to be studied. One significant problem is how to improve the outcomes of children who have widespread (metastatic) disease. Critical biological processes may play a role in the metastatic process, and by better understanding these processes it may be possible to disrupt the metastatic cascade that produces poor outcomes in children with cancer.

Little is known about natural killer (NK) cell activity in the very young. Evidence from recent studies showed that prepubescent (very young) rats with a reduced level of NK cell activity were more susceptible to tumor metastasis. The aim of this study was to further characterize NK cell activity and tumor resistance in prepubescent rats, specifically with respect to the effects of stress and sex, since these factors modulate tumor development in adult populations.

Advance: Natural killer cell activity was lower in prepubescent animals as compared to mature animals. When prepubescent rats were injected with cancer cells, they retained more than 10-times the number of cells in their lungs (an indicator of metastasis) as compared to adult rats. Unlike the adults the stress of surgery did not further increase the number of tumor cells that were retained. Stimulation of the "fight or flight" response of the nervous system using a drug did not suppress NK cell activity. This suggests that younger animals are less sensitive to the impact of changes in the sympathetic nervous system. Thus, neither surgery nor sympathetic nervous system stimulation enhanced cancer cell retention in the lung.

Implications: If replicated in humans, this animal model study will have important clinical implications. The study suggests that there are marked age differences in the NK cell responses to surgical stress and sympathetic nervous system stimulation and these differences may play a role in understanding the metastatic process in children.

Page GG, Ben-Eliyahu B: Natural killer cell activity and resistance to tumor metastasis in prepubescent rats: deficient baselines, but invulnerability to stress and ß-adrenergic stimulation. NeuroimmunoModulation, 7(3):160-7. 2000.

Influence of Physical Activity, Socioeconomic Status, and Ethnicity on Weight in Adolescents

Background: In the twenty plus years since the National Center for Health Statistics compiled its 1976-80 data, the incidence of obesity in children and adolescents has increased approximately six percent. The increased incidence was noted for both boys and girls and for all ethnic groups. This trend is a grave concern since obesity is linked to cardiovascular disease.

Data from various studies provide divergent opinions about the influence of physical activity on obesity in adolescents. The lack of a consistent relationship between physical activity and body weight could be related to several factors not accounted for in these studies, such as socioeconomic status and lack of precision in the measurement of physical activity. The purpose of this study was to examine the effects of physical activity and inactivity on the weight status of adolescents while taking into consideration their socioeconomic status, ethnicity and gender.

Advance: In a study of over 2,000 adolescents, investigators discovered that the time adolescents spent doing sedentary activities (such as watching TV and playing video games) did not relate directly to obesity if ethnicity and socioeconomic status were considered. For the girls, being white and having a moderate to high socioeconomic status reduced the risk of being overweight. For the boys, being white and participating in high intensity activities (soccer, basketball, etc.) for 15 minutes three times per week reduced the boys' risk of being overweight.

Implications: The fact that socioeconomic status and ethnicity predict obesity suggests that intervention programs should focus on lower socioeconomic status communities. The study also suggested a clear direction for interventions among adolescent boys, where using strategies to increase participation in high-intensity exercises (soccer, basket ball, swimming or running) may protect against obesity. To add this type of physical activity into the busy schedule of adolescents would require the participation of the school to improve physical education programs and intramural experiences. Another option might be to increase community recreation programs that incorporate opportunities for high-intensity physical activities for persons of limited skill. The study did not provide clear direction for the content of such programs for girls. The authors suggest that in girls dietary habits may be a more important than activity levels in the risk for obesity.

McMurray RG, Harrell JS, Shibing D, Bradley CB, Cox LM, Bangdiwala SI: The influence of physical activity, socioeconomic status, and ethnicity on the weight status of adolescents. Obesity Research, 8(2):130-9. 2000.

Eligibility for Managing Childhood Dehydration in Alternative Settings

Background: Although most children with gastroenteritis who live in developed countries have mild symptoms and little or no dehydration, a substantial number will have more severe disease. In the United States, an average of 220, 000 children younger than 5 years are hospitalized each year with gastroenteritis, accounting for more than 900, 000 hospital days. Hospitalization and outpatient care for pediatric diarrhea result in direct costs of more than $2.0 billion per year. There are also indirect costs to families when family routines are disrupted because of hospitalization.

Pediatricians are increasingly pressured to avoid hospitalizations. There are wide geographic variations in the pattern of hospitalizations for childhood dehydration, suggesting that some of the hospitalizations may be a precautionary measure and that care in an alternative setting might be possible. Alternative settings might include short-stay treatment centers, home care, and sick-child day care. Treating dehydration in alternative settings may avoid the need for hospital admission, decreasing costs and disruption to the family. The purpose of this study was to assess the number of children with dehydration who were admitted to hospitals in one county who might have been cared for in an alternative setting and to assess what type and duration of services would have been required to care for the children.

Advance: From a random sample of 380 medical records a sample of 276 children were identified as having dehydration without other major chronic illnesses as a contributing factor. The records of these children were evaluated. Overall, rehydration was achieved long before the children were discharged from the hospital, with much of the rehydration occurring in the emergency room. The average time it took for rehydration was 13.3 hours, and 90% of children were rehydrated within 24 hours of admission.

Implications: For most children who develop acute gastroenteritis, their care could be effectively managed outside of the hospital setting with a home nursing service that would be more cost effective and less traumatic to the family.

McConnochie KM, Conners GP, Lu E, Wilson C: How commonly are children hospitalized for dehydration eligible for care in alternative settings? Archives of Pediatric and Adolescent Medicine, 153(12):1233-41. 1999.

Coping Skills Training for Youth with Diabetes Mellitus

Background: The Diabetes Control and Complications Trial demonstrated that for patients over age 13, intensive therapy and better metabolic control can reduce the incidence and progression of microvascular and neuropathic complications by 27% to 76%. Thus achieving glycemic control is the goal of therapy. Adolescence is a particularly difficult time to achieve near normal blood glucose values, not only for physiological reasons but also because coping with the physical, emotional, and social demands of self-management of type 1 diabetes can be a formidable task.

The Adolescents Benefit from Control (ABCs) of Diabetes is a prospective, randomized controlled trial to examine whether a behavioral program of coping skills training in combination with intensive diabetes management will lead to improved metabolic and psychosocial outcomes in adolescents.

Advance: Over one year, a group of adolescents who received a behavioral intervention in conjunction with intensive diabetes management had better glycemic control and less impact of diabetes on their quality of life when compared to adolescents who had only an intensive diabetes management intervention. Females who received the behavioral intervention had a decreased incidence of weight gain and hypoglycemia. This finding was not seen in the male adolescents.

Implications: The addition of a behavioral intervention added an important aspect to the repertoire of activities adolescents can use to initiate and maintain intensive treatment of diabetes. The use of coping skills that help adolescents to negotiate with family members over treatment responsibilities and to negotiate treatment goals with the diabetes treatment team may be particularly helpful in achieving the goals of intensive therapy. Such skills are different from those required to simply manage diabetes and can be taught within the context of diabetes care.

Grey M, Boland EA, Davidson M, Li J, Tamborlane WV: Coping skills training for youth with diabetes mellitus has long-lasting effects on metabolic control and quality of life. Journal of Pediatrics, 137(1):107-13. 2000.

Early Invention to Improve Maternal and Infant Outcomes

Background: More than half a million adolescents give birth in the United States each year. Adolescent pregnancy and parenting issues remain a major concern because of their impact on maternal and child health and on the social and economic well-being of the nation. Early childbearing has been found to have negative effects on the health and life course of both mothers and infants.

Adverse health outcomes for this population are associated with late or absent prenatal care and with risky health behaviors such as poor nutritional habits and unsafe sex. Each year childbearing is directly responsible for the failure of 30,000 teenage girls to complete high school and early childbearing has an important relationship with transmission of poverty across generations. The purpose of this study was to evaluate the effects of an early intervention program that uses a public health nursing model on health and social outcomes of adolescent mothers and their children.

Advance: An early intervention program was compared to traditional public health nursing care in a group of young mothers, most of whom were underserved Latinas and African-Americans. The early intervention program provided 17 home visits from pregnancy through the infant's first year, whereas traditional care provided one or two home visits. The early findings from this longitudinal study demonstrated that both the early intervention and the traditional public health nursing care (supplemented with phone calls) resulted in rates of premature births lower than the national norm (11%). The rates of repeated hospitalizations after birth for the infants was comparable across groups, but the early intervention infants had fewer hospital days, suggesting that their mothers recognized problems earlier. The adolescents in the early intervention group were more likely than those in the traditional care group to stay in school. Substance abuse among young mothers continues to be a problem, with subjects in both groups reporting more alcohol and drug use after delivery than during pregnancy.

Implications: The findings support the effectiveness of public health nursing in improving perinatal outcomes for vulnerable adolescent mothers. With more intense and sustained intervention it may be possible to improve infant health and maternal education achievement of both Latinas and African-Americans. Interventions are needed to reduce alcohol and illicit substance use after childbirth and to help young mothers deal with their histories of childhood abuse.

Koniak-Griffin D, Anderson NLR, Verzemnieks I, Brecht ML: A public health nursing early intervention program for adolescent mothers: Outcomes from pregnancy through 6 weeks postpartum. Nursing Research, 49(3):130-8. 2000.

Long-Term Management of PMS Symptoms Using Nonpharmacological Interventions

Background: Premenstrual syndrome is the cyclic recurrence of distressing somatic and affective perimenstrual symptoms accompanied by behavioral changes that can result in deterioration of interpersonal relationships and personal health and function. A woman's experience of perimenstrual symptoms have been found to reduce work efficiency, increase absenteeism, and negatively impact family and personal relationships.

The cause of the syndrome remains unclear. With no clear diagnostic test or singular treatment, symptom assessment and management has been the common approach to diagnosis and treatment of premenstrual syndrome. Nonpharmacological symptom management strategies have not been tested with the same rigor as medications. The purpose of this study was to determine the short and long term effectiveness of a nonpharmacological treatment aimed at relieving the symptom severity and distress associated with premenstrual syndrome.

Advance: This study is one of the first attempts to determine the long-term effectiveness of multiple nonpharmacological interventions to treat premenstrual syndrome. The intervention allowed women to choose from among multiple strategies to relieve symptoms. Professional and peer support was provided as they monitored their symptoms and used diet, exercise, and behavioral, cognitive, and stress management techniques to relieve symptoms. Data were collected five times over 18 months. The intervention reduced symptom severity by 75%. Premenstrual depression was reduced by 30-54% which compares favorably to the 40-52% reduction in depression associated with antidepressant medication reported in the literature. Symptom improvements associated with the intervention were maintained or enhanced over time.

Implications: Since premenstrual syndrome can be considered a chronic recurring, and stress-related condition that requires multiple treatment strategies, the intervention may be useful with other women's health problems that are stress related.

Taylor D: Effectiveness of professional-peer group treatment: symptom management for women with PMS. Research in Nursing & Health, 22(6):496-511. 1999.

Description of Herpes Simplex Virus Movements in Nerves May Lead to New Treatments

Background: Herpes simplex virus is a leading cause of blindness in the US. After initially infecting mucous membranes in the mouth or the cornea of the eye, the virus moves into sensory nerve endings and travels relatively long distances through the axon to the nerve cell body. Some nerve cell populations allow the virus to enter a dormant (latent) state that persists for the life of the infected individual. Reactivation of the latent virus occurs periodically and can lead to reappearance and potential spread of virus on the surface of the eye. Repeated cycles of latency-reactivation cause progressive scarring and clouding of the cornea that, in turn, leads to blindness. Although a number of studies have focused on the molecular characterization of latency and reactivation, little information is available about the movement of virus from the cornea to nerve cell bodies and, after reactivation, back to the cornea.

Advance: Researchers now can follow the movements of virus in both directions. A model was developed by injecting a known quantity of virus directly into a cluster of nerve cell bodies permitting researchers to examine the time course of reactivation and spread of the virus. Movement of virus from the nerves to the corneal epithelial cell layers has a distinct pattern: the virus leaves the nerve endings, enters the middle layers of epithelial cells, and then preferentially spreads outward into the tears. Similarly, movement of virus toward the cell body was directly observed and indicated that certain viral components are essential for transport to the nerve cell body and therefore establishment of latency.

Implications: Reactivation of latent virus leads to destruction and sloughing of the outer epithelial cell layers and facilitates infection of new host cells. Learning how virus is transported from the epithelium to the nerve cell body or vice versa may lead to treatments that inhibit this process and thus prevent recurrent disease and scarring. Researchers will also be able to examine the gene products that are essential to viral release from nerves, the genes involved in the spread of virus between the cells of the epithelium, and the transport machinery that mediates these movements. Any or all of these new sites may be amenable to new therapies that would prevent latency-reactivation, spread of the virus, and scarring of the cornea.

Ohara PT, Chin MS, LaVail JH: The spread of herpes simplex virus type 1 from trigeminal neurons to the murine cornea: an immunoelectron microscopy study. Journal of Virology, 74(10):4776-86. 2000.

Bearer EL, Breakefield XO, Schuback D, Reese TS, LaVail JH: Retrograde axonal transport of herpes simplex virus: evidence for a single mechanism and a role for tegument. Proceedings of the National Academy of Sciences, 97(14):8146-50. 2000.

Gene Therapy for Sight-threatening Uveitic Disease

Background: Autoimmune diseases, including some types of uveitis, are caused by the immune system attacking its own tissues. The cause is thought to be a defect in recognition of self tissue components (antigens) as "self" either during maturation of the immune system, or subsequently. This results in persistence of specific white blood cells known as lymphocytes. These lymphocytes are capable of responding to components of self that would normally be eliminated or held in check in healthy individuals. Upon being triggered by inflammatory processes or by microorganisms having structures immunologically similar (crossreactive) to self, these lymphocytes can become activated and begin to attack the tissues. B cells are a group of immunologically important lymphocytes responsible for producing antibodies. The disease-causing lymphocytes belong to another lymphocyte subpopulation known as T cells. Normally, a T lymphocyte becomes tolerant when it "sees" its antigen in a non-stimulatory manner. It then becomes unable to respond (anergic) or dies a programmed cell death (deleted). In the case of antigens derived from the eye, persistence of lymphocytes capable of responding to retinal antigens can lead to severe autoimmune retinal disease and ultimately blindness.

Advance: Researchers at the NIH in collaboration with scientists from the American Red Cross devised an approach to reinstate functional tolerance to a retinal antigen and tested it in a mouse model of uveitis that represents sight-threatening human uveitic disease. The idea was to "reeducate" the immune system to tolerate the retinal antigen by presenting it in a fashion that would lead to anergy or deletion of the responding T lymphocytes. Gene therapy using B cells infected with a genetically engineered retrovirus was employed and found to protect the recipient mice from uveitis elicited by a challenge with the retinal antigen. Importantly, mice that were challenged for uveitis first and given the therapeutic regimen later, to more closely simulate a clinical situation, could also be protected.

Implications: Because sight-threatening autoimmune uveitis in humans is thought to be caused by similar mechanisms as the experimental disease in mice, this kind of therapy could be adapted to a clinical setting using retinal antigens to which responses are present in human patients. Additionally, the B cells "infected" with the engineered retrovirus do not retain the virus itself but only the gene(s) that it carries. This suggests that infusion of treated cells back into the body would largely circumvent the known drawbacks of infusing the engineered virus itself. A therapy that protects eye tissues from development of uveitis, as well as after development of uveitis, may provide a new approach for treatment of established autoimmunity where patients come to the clinic with an ongoing disease.

Agarwal RK, Kang Y, Zambidis E, Scott DW, Chan CC, Caspi RR: Retroviral gene transfer with an immunoglobulin-antigen fusion construct protects from experimental autoimmune uveitis. The Journal of Clinical Investigation, 106(2):245-52. 2000.

Oxygen Restrictions and Retinopathy of Prematurity

Background: Many premature infants need supplemental oxygen soon after birth because their lungs are not sufficiently mature to efficiently transfer oxygen into their bodies. Researchers have long known that supplemental oxygen, while helping infants survive, might increase cases of retinopathy of prematurity (ROP). ROP develops in very premature infants when abnormal blood vessels grow and spread throughout the retina, the nerve tissue that lines the back of the eye. The scarring and bleeding caused by the excess growth of these blood vessels can lead to retinal detachment, resulting in vision loss. ROP develops in about 14,000-16,000 infants each year who weigh less than 2 3/4 pounds (1250 grams) at birth. In most cases (80 percent), the disease improves and leaves no permanent damage. However, about 1,100-1,500 infants annually develop ROP that is severe enough to require surgical treatment, which usually will stop the growth of abnormal blood vessels and prevents retinal detachment. Even with these therapies, about 400-600 infants with ROP become legally blind each year.

Advance: Recent research had suggested that controlled amounts of supplemental oxygen might actually keep ROP from progressing from moderate to severe. If controlled amounts of supplemental oxygen could help prevent the progression of ROP, then infants could avoid this threat to their sight and consequently the invasive surgery for severe ROP, with its possible long-term side effects. In order to test the safety and efficacy of providing infants supplemental oxygen, the NIH supported the Supplemental Therapeutic Oxygen for Pre-threshold ROP (STOP-ROP) study. Researchers found that modest supplemental oxygen given to premature infants with moderate cases of retinopathy of prematurity (ROP) may not improve ROP, but definitely does not make it worse.

Implications: The results mean that clinicians do not have to be as restrictive as they have been when giving supplemental oxygen to infants who have already developed moderate ROP.

The STOP-ROP Multicenter Study Group: Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. Pediatrics, 105(2):295-310. 2000.

HIV Strains Responsible for Today's AIDS Epidemic Dated to Early 20th Century

Background: In 1983, scientists identified the human immunodeficiency virus (HIV-1 and HIV-2) as the causative agent of acquired immunodeficiency syndrome (AIDS). Current evidence suggests that HIV-1 was transmitted to humans from chimpanzees infected with the simian immunodeficiency virus (SIV), the analog of HIV in apes and monkeys. Until now, it was not clear when HIV-1, specifically the strain called HIV-1 main (also called HIV-1 M group), first appeared in humans. Transmission of pathogens from animal to humans is called zoonosis when this transfer leads to disease. Other examples of zoonotic transfer include rabies, Ebola virus, and Marburg virus. However, few viruses have been as readily accepted by the host species as HIV-1 M, which is the most prevalent type of HIV having infected nearly 50 million people, and killing 16 million more, worldwide. Previous attempts to estimate the age of a common ancestor and the time of spread for HIV-1 M have been impeded by limited availability of HIV-1 genetic sequencing data that predate the discovery of HIV in 1983 and by limits in computational power.

Advance: Using supercomputers and known sampling dates of virus from humans, and assuming a constant rate of evolution of HIV, investigators have estimated that the introduction of HIV-1 M to humans and its subsequent expansion occurred around 1931, much earlier than previously speculated. This result rebuts the hypothesis that HIV-1 was introduced into the human population through contaminated oral polio vaccinations administered in Central Africa between 1957 and 1960.

The methodology used to determine the date of emergence of last common ancestor of HIV-1 is an advance as well. The methodology developed for this study helps bioinformatics keep pace with the rapid growth in known DNA sequences. (Bioinformatics are the tools and techniques involved in collecting, storing, and analyzing genetic information.) By extending established algorithms and adapting codes for use on parallel supercomputers the researchers enabled application of sophisticated evolutionary models to the large HIV-1 sequence data sets. The validity of their approach and the soundness of their assumptions were tested by correctly estimating the timing of two historically-documented biological events.

Implications: Insight into the origin and evolution of HIV-1 could help explain the conditions that contributed to the AIDS pandemic and why the movement of this pathogen between species had a more devastating outcome than other occurrences of zoonotic infection. Additionally, the analysis provides insight into the spread of HIV-1, the most prevalent type of HIV worldwide. And finally this information may be useful in developing ways to prevent the spread of other infectious diseases in the future.

Furthermore, the tools developed here can be applied to other problems. The tools extend the power to simultaneously analyze large data sets representing many different organisms. The tools also could be used to analyze multiple genes from another highly-variable pathogen.

Korber B, Muldoon M, Theiler J, et al: Timing the ancestor of the HIV-1 pandemic strains. Science, 288(5472):1789-96. 2000.

Vaccine Candidates for *Plasmodium falciparum* and *Plasmodium vivax* Obstruct Parasite Invasion of Red Blood Cells

Background: Malaria, one of the world's most deadly tropical diseases, kills over 1 million people each year, mostly young children. Every year about 275 million people develop malaria. The need for an effective malaria vaccine has become ever more important with the spread of drug resistant malaria. The causative agents are four species of unicellular parasites: *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale,* and *Plasmodium malariae*. Of these, *P. falciparum* accounts for a large majority of deaths and is the most dangerous clinically. Plasmodia have a complex life cycle consisting of multiple stages of development in both humans and in the mosquito. The stages in humans occur in the liver and the red blood cells. Blocking at either stage could prevent disease. Investigators are now exploring several vaccine candidates for *P. falciparum* and *P. vivax* that aim to block the parasite's invasion of the red blood cells. Each parasite has a different host receptor protein that it uses to make contact with the red cells (enabling invasion and infection). In *P. falciparum* and *P. vivax,* the parasite proteins involved in red cell binding are known, respectively, as Duffy-binding protein (DBP) and erythrocyte-binding antigen (EBA-175).

Advance: NIH-supported investigators have shown that specific antibodies can prevent *P. falciparum* from entering human red blood cells. Investigators injected a synthetic form of EBA-175 into mice and then isolated the antibodies they produced. They then showed that the isolated antibodies can block *P. falciparum* invasion of human red cells. *P. falciparum* parasites appear capable of invading red cells by two different pathways, one of which involves binding to a sugar-containing structure, sialic acid, on the red cell surface and one of which appears to be independent of sialic acid binding. The antibodies directed against the synthetic EBA-175 block both of these pathways of red cell invasion. In a related set of experiments, another team of NIH investigators demonstrated that antibodies to *P. vivax* inhibit biding of DBP to red cells. Some people who live in regions with high rates of *P. vivax* malaria are clinically immune to that disease. The investigators demonstrated that serum (the portion of blood in which antibodies are present) extracted from such individuals inhibits binding of DBP to red cell. The investigators obtained similar results when they repeated this experiment using sera from animals pre-exposed to a synthetic version of DBP.

Implications: This research has important implications for the development of an effective vaccine against blood-stage malaria. Taken together, these findings on *P. falciparum* and *P. vivax* suggest that vaccines designed to elicit immune responses that target members of the DBP/EBA-175 family can inhibit an essential biological function of different malaria parasites.

Narum DL, Haynes JD, Fuhrmann S, et al: Antibodies against the *plasmodium falciparum* receptor binding domain of EBA-175 block invasion pathways that do not involve sialic acids. Infection and Immunity, 68(6):1964-8. 2000.

Liang H, Narum DL, Fuhrmann SR, Luu T, Sim BKL: A recombinant baculovirus-expressed *plasmodium falciparum* receptor-binding domain of erythrocyte binding protein EBA-175 biologically mimics native protein. Infection and Immunity, 68(6):3564-8. 2000.

Michon P, Fraser T, Adams JH: Naturally acquired and vaccine-elicited antibodies block erythrocyte cytoadherence of the *plasmodium vivax* duffy binding protein. Infection and Immunity, 68(6):3164-71. 2000.

The Effects of El Nino on Severe Diarrheal Diseases in Peruvian Children

Background: The El-Nino phenomenon, the warming of the Pacific Ocean that occurs every two to seven years, has been linked to outbreaks of dengue fever, malaria, and cholera, but its effects on the epidemiology of non-cholera diarrhea have not been well studied.

Advance: A team of researchers from the Johns Hopkins School of Public Health and their colleagues at A.B. PRISMA and the Instituto Nacional de Salud in Lima, Peru, examined diarrheal disease hospital records for over 57,000 children from 1993-1998 to assess the correlation between weather patterns and incidences of childhood diarrhea. Admissions during the El Nino season increased significantly above expected norms – by 200 percent in 1997-1998 alone. The researchers estimate that hospital admissions due to diarrheal disease increased by more than eight percent with every one degree centigrade rise in temperature.

Implications: These results suggest that diarrheal disease cases could potentially increase by millions worldwide with each degree of increase in ambient temperature due to global warming and other local factors. Since diarrhea already causes one billion disease episodes and 3 million deaths annually in children under 5 years old worldwide, understanding the effects of weather variability on the epidemiology of infectious diseases can be an important factor in planning preventive public health strategies in advance of future El Nino episodes.

Checkley W, Epstein L, Gilmam RH, et al: Effects of el nino and ambient temperature on hospital admissions for diarrhoeal diseases in peruvian children. The Lancet, 355(9202):442-50. 2000.

Mapping Heroin Trafficking Routes Predict HIV Transmission.

Background: Heroin availability, needle sharing, and unsafe sex have been identified as risk factors for HIV-1 transmission among IV drug users and their partners. Programs to reduce unsafe practices related to drug paraphernalia and sex have been effective in reducing HIV transmission among IV drug users and their partners. The "Golden Triangle" region of Thailand, Burma and Laos is well known as a major heroin producing area, and trafficking is routed through China, Vietnam and India. Scientists have used information from the narcotics control literature, published studies on HIV prevalence, and information from key informants to link four main trafficking routes in the "Golden Triangle" region of Thailand, Burma and Laos.

Advance: Four recent outbreaks of HIV-1 among IV drug users appear to be linked to trafficking routes. The combinations of subtypes of HIV infections differ among these four routes, indicating that these are separate and unlinked outbreaks. The scientists identified "self-testing drugs" in which drugs and drug paraphernalia are shared by the local traffickers as a probable mode of cross-border transmission of HIV.

Implications: By mapping heroin trafficking routes and probable transmission modes, increased transmission of HIV-1 among intravenous drug users in towns and cities along these routes can be predicted and appropriate prevention strategies developed.

Beyrer C, Razak MH, Lisam K, Chen J, Lui W, Yu XF: Overland heroin trafficking routes and HIV-1 spread in South and South-east Asia. AIDS, 14(1):75-83. 2000.

Mother-to-child Transmission of HIV Infection Through Breast Feeding

Background: While the risk of transmission of HIV infection through heterosexual or blood transfusion has been documented in observational studies, only estimates are available for the proportion of HIV infection in newborns due to breast feeding. These estimates vary from 5-25%. The need to better estimate the rate and understand the factors that influence transmission through breast milk is very critical since breast feeding is feasibly the only source of nutrition for many infants in resource-poor countries.

Advance: A study in Kenya (Nduati et al), in which pregnant HIV-infected women were randomized to breast feed or to formula feed, found that the infants born to mothers in the breast feeding group were more likely to become HIV infected (37%) than infants born to mothers in the formula feeding group (21%). Forty four percent of the HIV infections in the infants born to mothers in the breast feeding group were due to breast milk. Most of the infections due to breast feeding occurred within the first six months of life. While formula feeding appears to be the best choice for HIV infected women to prevent breast milk transmission, breast feeding is the social, cultural and economic norm in many resource-poor countries. While 96% of the mothers who were assigned to breast feeding group did so, 70% of the women assigned to formula feeding group breast fed their infants.

Implications: By randomizing women to either breast or formula feeding, this study was able to estimate the risk of HIV transmission through breast feeding without the potential bias of observational studies. Although the Kenya study was not able to differentiate those infants who received mixed feeds from those who had only received breast milk, data from an observational study in South Africa (Coutsoudis et al) suggests that "mixed feeding" is the most likely infant feeding practice that increases transmission of HIV. More studies are underway to further clarify this complex issue so that recommendations to reduce post-delivery HIV infection can be developed.

Nduati R, John G, Mbori-Ngacha D, et al: Effect of breast feeding and formula feeding on transmission of HIV-1: a randomized clinical trial. The Journal of the American Medical Association, 283(9):1167-74. 2000.

Coutsoudis A, Pillay K, Spooner E, Kuhn L, Coovadia HM: Influence of infant feeding patterns on early mother-to child transmission of HIV-1 in durban south africa: a prospective cohort study. The Lancet, 354(9177):471-6. 1999.

Protein Found During Pregnancy Predicts Preterm Birth

Background: Fibronectins are a family of proteins found in the blood and on the surface of some cells. Fetal fibronectin (FFN), which is located in the intrauterine space between the fetus and mother, appears to have a role in implantation of the early fertilized egg and in the development of the placenta. Since FFN is unique to pregnancy, researchers have studied levels in vaginal secretions as a marker of abnormal pregnancy outcome. Recently, a study was undertaken to evaluate if FFN found in vaginal secretions early in pregnancy was associated with subsequent preterm birth.

Advance: First, researchers screened 13,360 pregnant women for the presence of FFN during the late first and early second trimester. After following these women through their pregnancy, the researchers determined whether those women who had given birth prematurely had been previously identified as having FFN present in their vaginal secretions. The data showed that pregnant women with a vaginal FFN level greater than the 90th percentile had a 4-fold increased risk of spontaneous preterm birth occurring at less than 28 weeks gestation.

Implications: In addition to providing a method for identifying patients who are at significant risk for preterm delivery, these findings shed light on a critical mechanism underlying spontaneous preterm birth. These findings also support the concept that at least a portion of preterm delivery is a chronic pregnancy condition that begins in the first trimester. Preterm birth complicates 8-10 percent of all pregnancies in the United States and is the leading cause of infant morbidity and mortality. Current estimates show that the annual direct cost of caring for premature infants in the United States is over 2 billion dollars. In addition, prematurity occurs disproportionately in African-American infants. Using tests to detect FFN may allow researchers to develop strategies to prevent prematurity, as well as reduce health disparities in infant morbidity and mortality.

Goldenberg RL, Klebanoff M, Carey JC, et al: Vaginal fetal fibronectin measurements from 8 to 22 weeks' gestation and subsequent spontaneous preterm birth. American Journal of Obstetrics and Gynecology, 183(2):469-75. 2000.

SCIENCE CAPSULES

Ignition-Lock Device Prevents Drunk Driving. Interlocks are devices that test a driver's breath and prevent his or her car from starting if the device detects alcohol over a minimal level. New research confirms that, when installed, interlocks work quite effectively to deter people convicted of driving under the influence (DUI) from committing repeat offenses. Furthermore, DUI offenders who use interlocks make fewer subsequent attempts at driving with breath alcohol levels that are too high if counselors have given them brief motivational sessions and educated them about the interlock. Few offenders elect to install the devices, however, and once the device is removed, the interlock drivers have repeat DUI rates similar to those of other offenders. Nevertheless, this research holds clear policy implications, in that the risk to the public would be substantially reduced if courts could find ways to increase participation rates in interlock programs and thus keep the roads safer, at least during court-imposed interlock periods.

Voas RB, Marques PR, Tippetts AS, Bierness D: The alberta interlock program: the evaluation of a province-wide program on DUI recidivism. Addiction, 94(12):1849-59. 1999.

Marques PR, Voas RB, Tippetts AS, Bierness DJ: Behavioral monitoring of DUI offenders with the alcohol ignition interlock recorder. Addiction, 94(12):1861-70. 1999.

Male-Female Differences in Drug Use Traced to Differences in Opportunity to Use. It has been theorized that males have higher rates of drug use than females because males have a greater chance of progressing from initial opportunity to use a drug to actual drug use. In assessing data from 131,226 respondents to the 1979 to 1994 National Household Survey on Drug Abuse, researchers found that males age 12 and older did have more initial opportunities to use drugs than females of the same age. But the data showed that once an opportunity had occurred few male-female differences existed in the probability of making a transition into drug use. These results support the theory that males have higher rates of drug use because they have a greater number of initial opportunities to use drugs, as well as a higher probability of progressing to actual drug use. Thus, sex differences emerge in the earliest stages of drug involvement.

Van Etten ML, Neumark YD, Anthony JC: Male-female differences in the earliest stages of drug involvement. Addiction, 94(9):1413-9. 1999.

Seniors' CAM Habits Reinforce Necessity of Physician-Patient Dialogue. Contemporary studies of complementary and alternative medicine (CAM) practices estimate that 42 percent of all adults in the United States use some form of CAM. New findings from a survey of senior citizens confirm that the extent of their CAM use closely mirrors that of the population at large. Results from this study of Medicare beneficiaries found that more than 40 percent reported using CAM. Of those using

CAM, some 80 percent maintained that they experienced substantial benefit from it. However, the majority did not disclose their use of CAM therapies to their physicians. These findings underscore the need for conventional physicians to inquire about CAM use by their elderly patients.

Austin JA, Pelletier KR, Marie A, Haskell WA: Complementary and alternative medicine use among elderly persons; one-year analysis of a blue shield medicare supplement. Journal of Gerontology, 55A(1):M4-9. 2000.

CAM use in Cancer Patients. Most oncologists are aware that patients commonly use complementary and alternative medicine (CAM) in conjunction with cancer therapy, yet few discuss these therapies with their patients. A recent survey of patients showed that nearly 85 percent employed at least one CAM therapy while undergoing conventional oncology treatment. This underscores the value of patient-provider communication and the need to study various combinations of cancer and CAM therapies.

Richardson MA, Sanders T, Palmer JL, Greisinger A, Singletary SE: Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology. Journal of Clinical Oncology, 18(13):2505-14. 2000.

Video Series Helps Parents Improve Infant Health. New parents often lack accurate and reliable information about their infant's health and development. To help new parents, scientists developed "My Baby U," a research-based home video series that bridges this critical information gap. The researchers found that not only did young parents who viewed the series gain significantly more knowledge about infant health and development than did parents in the control group, but their infants also experienced fewer severe illnesses and required far fewer medical services than did the control infants. The findings suggest that, with proper education and by improving parents' understanding of their infants' needs, significant strides can be made in improving outcomes while lowering pediatric health care costs.

Brown M, Yando R, Rainforth M: Effects of an at-home video course on maternal learning, infant care and infant health. Early Child Development and Care, 160:47-65. 2000.

Researchers Find Important Protective Immune Differences in HIV-Infected and Uninfected Women. The mucosal immune system is the first line of defense against infection in the female reproductive tract, yet scientists know little about how this system is regulated. Investigators found significant differences between levels of immune hormones in the vaginal secretions of HIV-infected and uninfected adolescent girls. In addition, the data showed that infection with both HIV and the human papillomavirus, which can cause severe gynecologic conditions in women, greatly affected the concentrations of these immune hormones. The investigators suggest that a better understanding of these differences could provide the basis for developing effective immunizations to protect women from genital tract infections, including HIV and other sexually transmitted diseases.

Crowley-Nowick PA, Ellenberg JH, Vermund SH, Douglas SD, Holland CA, Moscicki, AB: Cytokine profile in genital tract secretions from female adolescents: impact of human immunodeficiency virus, human papillomavirus, and other sexually transmitted pathogens. The Journal of Infectious Diseases, 181(3):939-45. 2000.

Relationship With Mothers Influences Teen Sexual Behavior. Examining data from the National Longitudinal Study of Adolescent Health, researchers showed that adolescent boys or girls were three times more likely to engage in sex, if they reported low satisfaction in their relationships with their mothers, than if they were highly satisfied with the relationship. In addition, teens who perceive that their mothers disapprove of engaging in sex are less likely to do so and, therefore, less likely to become pregnant. Conversely, teens who perceived that their mothers had permissive attitudes were six times more likely to engage in such behaviors. However, teens also underestimated their mother's disapproval. Based on the findings, the researchers conclude that it is important to improve parent education, especially for mothers – who commonly engage in most of the daily interactions with their children. Such education would include communication techniques and parenting practices that not only strengthen the parents' relationships with their teens, but can influence their teens' sexual choices.

Dittus PJ, Jaccard J: Adolescents' perceptions of maternal disapproval of sex: relationship to sexual outcomes. Journal of Adolescent Health, 26(4):268-78. 2000.

HIV Infection Does Not Increase Complications From Cesarean Delivery. Since the immune system in women infected with HIV is compromised, scientists examined whether these women were at increased risk for complications after cesarean delivery. Scientists found that complications such as endometritis and wound infection after cesarean delivery in HIV-infected women were not significantly higher than in women who were not infected. Because cesarean delivery is a widely used procedure to reduce the risk of passing HIV from mothers onto their infants, this finding is of particular importance since it suggests that HIV-infected women can protect their infants from acquiring HIV without jeopardizing their own health.

Watts HD, Lambert JS, Stiehm ER, et al: Complications according to mode of delivery among human immunodeficiency virus-infected women with CD4 lymphocyte counts of ?500/muL. American Journal of Obstetrics and Gynecology , 183(1):100-7. 2000.

Exposure to Allergens During Infancy May Prevent a Lifetime of Allergic Asthma. The "hygiene hypothesis" contends that early, normal exposure to infectious organisms or other allergens causes the immune system to respond normally, while minimal exposure causes the immune system to become highly sensitized, leading to an allergic asthmatic response when exposure occurs later in life. Researchers showed that chronic exposure to common house dust containing a bacterial product known as endotoxin decreases the later risks of having an asthmatic response to this allergen. Infants who had little exposure to this allergen, because of cleaner homes, were more likely to develop an allergic response when later exposed. This suggests that normal exposure to environmental allergens early in life is a good thing and may be necessary for normal immune system development. It also argues against

current theories which hold that children deemed at-risk for developing asthma should be kept in an allergen-free environment.

Gereda JE, Leung DYM, Thatayatikom A, et al: Relation between house-dust endotoxin exposure, type 1 T-cell development, and allergen sensitisation in infants at high risk of asthma. The Lancet, 355(9216):1680-3. 2000.

Infection Rates Decrease Among U.S. Blood Donors. A recent study revealed that screening questionnaires and educational efforts implemented in 1992 are improving the safety of the United States blood supply. The already low prevalences of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) in blood collected from new donors decreased by half (0.030% to 0.015%) for HIV and by a third (0.63% to 0.40%) for HCV between January 1991 and December 1996. The rates among new donors are lower than those of the general population, indicating that screening potential donors for behavioral risk factors is effective in preventing the donation of infectious blood.

Glynn SA, Kleinman SH, Schreiber GB, et al: Trends in incidence and prevalence of major transfusion-transmissible viral infections in US blood donors, 1991 to 1996. The Journal of the American Medical Association, 284(2):229-35. 2000.

Researchers Identify a Potential Therapeutic Compound for Reducing Stroke Damage. Although some stroke patients are treated with tissue-type plasminogen activator (tPA), the treatment can cause serious complications if tPA leaks from the blood vessels into the brain cells. Scientists recently demonstrated that brain cells can reduce damage from tPA by producing an inhibitor called neuroserpin. Experiments in rats revealed that injecting neuroserpin immediately after a stroke reduces brain cell injury and death, indicating that neuroserpin has potential as a therapeutic agent.

Yepes M, Sandkvist M, Wong MKK, et al: Neuroserpin reduces cerebral infarct volume and protects neurons from ischemia-induced apoptosis. Blood, 96(2):569-76. 2000.

Hostility may be Associated with Early Atherosclerosis. Researchers studying men and women who were 18-30 years of age when initially evaluated found that hostility was strongly correlated with subsequent coronary calcification, a measure of subclinical (undetected) coronary artery atherosclerotic disease. This association persisted even when demographic, lifestyle, and physiological variables were taken into account. This finding suggests that early psychosocial interventions may have an important role in prevention of heart attacks.

Iribarren C, Sidney S, Bild DE, et al: Association of hostility with coronary artery calcification in young adults. The Journal of American Medical Association, 283(19):2536-51. 2000.

Reducing Children's Television Viewing May Prevent Obesity. A school-based study involving third and four-grade children used a 6-month classroom curriculum to encourage reduced use of television, videotape, and video games. Compared with controls, students in the intervention group benefitted by showing significant decreases in several measures of body fatness. The findings suggest a

feasible approach to address the alarming trend toward obesity that is occurring among U.S. children and adolescents.

Robinson TN: Reducing children's television viewing to prevent obesity. A randomized clinical trial. The Journal of the American Medical Association, 282(16):1561-7. 1999.

Older (and Cheaper) Blood Pressure Drug Holds its Own. In recent years newer, often expensive anti-hypertensive drugs have been widely prescribed. Although they do a good job of lowering blood pressure, their ability to reduce cardiovascular events (e.g., heart attacks) has not been demonstrated. A large clinical trial that is comparing a diuretic with three types of newer drugs, including an alpha-adrenergic blocker, recently found that the diuretic was superior to the alpha-adrenergic blocker in terms of its ability to reduce the overall incidence of cardiovascular disease events, and particularly incidence of congestive heart failure, in patients over 55 years of age. This finding provides valuable information for physicians seeking to prescribe the best and most cost-effective drugs for their patients.

The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone. The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). The Journal of the American Medical Association, 283(15):1967-75. 2000.

Risk of Antibiotic Treatment of *E. coli O157:H7* Infection. *E. coli O157:H7* is a foodborne pathogen that causes severe hemorrhagic gastrointestinal infections. Approximately 15 percent of children with *E. coli O157:H7* infection also develop the hemolytic uremic syndrome (HUS) which, in its most severe form, can result in kidney failure and death. HUS appears to be due to a toxin (Shiga toxin) produced by the *E. coli* that can be absorbed into the blood stream during the acute gastrointestinal infection and that can cause widespread injury to endothelial cells, particularly in the kidney. Children with acute, febrile gastrointestinal illnesses are often treated with antibiotics; whether this is helpful or harmful in *E. coli O157:H7* infection has not been known. The researchers analyzed results from their large, ongoing, population-based database on *E. coli* infections for the possible role of antibiotics in HUS. They found that children treated with antibiotics during the acute gastrointestinal illness had a higher risk of developing HUS. The investigators hypothesized that the antibiotics led to lysis of the *E. coli O157:H7* in the colon and release of Shiga toxin with subsequent absorption and damage to endothelial cells. This important epidemiological study clearly shows that children with acute gastrointestinal illnesses should not receive antibiotics. The study also points to new directions in elucidating the mechanisms by which Shiga toxin is absorbed and causes damage after *E. coli O157:H7* infection. [secondary – treatment]

Wong CS, Jelacic S, Habeeb RL, Watkins SL, Tarr PI: The risk of the hemolytic-uremia syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. The New England Journal of Medicine, 342(26):1930-6. 2000.

Walking Reduces Risk of Type 2 Diabetes in Women. Obesity and reduced physical activity are major risk factors for the development of type 2 diabetes. People at risk for developing type 2 diabetes

are encouraged to maintain a healthy diet and engage in regular exercise. Using a cohort of women previously identified through the Nurses' Health Study, researchers examined the relationship between physical activity and the incidence of type 2 diabetes and further compared the role of moderate *versus* vigorous physical activity. They found that moderate forms of exercise, such as walking, as well as vigorous forms of activity such as aerobics, are both associated with a substantial reduction in risk of type 2 diabetes in women. This finding is a practical approach to prevention because walking is a form of exercise that is highly accessible, readily adopted, and rarely associated with injury.

Hu FB, Sigal RJ, Rich-Edwards et al: Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. The Journal of the American Medical Association, 282(15):1433-9. 1999.

Predictors of Smoking Cessation in Adolescents. It is estimated that over one third of American high school students are current smokers. NIH-supported researchers identified five factors that predict quitting smoking among adolescent smokers: Being an occasional (rather than daily) smoker; never having quit smoking, or previously quitting for more than 14 days; not having a mother who smoked; assuming they would not be smoking one year later; and demonstrating few symptoms of depression. These findings could be used to help tailor cessation programs to more effectively help adolescents quit smoking.

Zhu SH, Sun J, Billings SC, et al: Predictors of smoking cessation in U.S. adolescents. American Journal of Preventive Medicine, 16(3):202-7. 1999.

New Guidelines for Treating Tobacco Use and Dependence. Despite ample documentation of the long-term health effects of cigarette smoking, an estimated 48 million U.S. adults currently smoke. In 1997 (the most recent year for which data are available), approximately 40 percent of every-day smokers surveyed had attempted to quit in the previous 12 months. The NIH participated in the development of a U.S. Public Health Service Report, *Treating Tobacco Use and Dependence: A Clinical Practice Guideline*, which provides specific, evidence-based recommendations for brief and intensive tobacco cessation interventions and changes in the systems designed to promote the assessment and treatment of tobacco use. This guideline, which is updated from a 1996 document, describes clinical approaches and effective interventions for physicians to use with patients in various stages of readiness to quit smoking. The use of successful smoking cessation interventions will ultimately reduce the burden of illness, death, and economic cost resulting from tobacco use.

Fiore MC, Bailey WC, Cohen J, et al. A clinical practice guideline for treating tobacco use and dependence. The Journal of the American Medical Association, 283(24):3244-54. 2000.

Fiore MC, Bailey WC, Cohen SJ, et al. Treating Tobacco Use and Dependence: Clinical Practice Guideline. Rockville, MD: US Department of Health and Human Services, 2000.

Lack of Effect of Dietary Fiber on Recurrence of Colorectal Adenomas. Dietary factors have long been epidemiologically associated with reduced risks of colorectal cancer and colorectal adenomas, which can be precursors of cancer. In a recent study, 1429 patients with a history of colorectal adenomas received either 13.5 grams or 2 grams of wheat bran fiber per day for 34 to 36 months. At the end of the study, there was no difference between the two groups in the presence or absence of new adenomas, indicating that dietary supplementation of wheat bran fiber does not protect against recurrent colorectal adenomas.

Alberts DS, Martinez ME, Roe DJ, et al: Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. The New England Journal of Medicine, 342(16):1156-62. 2000.

Breast Cancer Risk after Surgical Removal of the Ovaries in BRCA1 Mutation Carriers. Women with certain mutations of the BRCA1 gene are at increased risk of developing breast or ovarian cancer. Researchers found that surgical removal of the ovaries (bilateral prophylactic oophorectomy) reduced the risk of breast cancer among women with BRCA1 mutations by approximately half; this risk reduction was even greater five to ten years after surgery. The researchers hypothesize that decreases in ovarian hormone exposure may be responsible for the decreased risk. These findings have important implications for the management of breast cancer risk in women who carry BRCA1 mutations.

Rebbeck TR, Levin AM, Eisen A, et al: Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. Journal of the National Cancer Institute, 91(17):1475-9. 1999.

Weighing the Risks and Benefits of Tamoxifen Treatment for Preventing Breast Cancer. Tamoxifen has been shown to decrease the risk of breast cancer among women at elevated risk, but the drug also has some serious side effects, including an increased risk of endometrial (uterine) cancer, stroke, and blood clots in the lung and/or the large veins. NIH researchers undertook a study to identify women for whom tamoxifen's benefits outweighed the risks. They found that the risks and benefits of tamoxifen depend on a woman's age, race, and specific risk factors for breast cancer. Overall, tamoxifen appears most beneficial for young women with an elevated risk of breast cancer.

Costantino JP, Gail MH, Pee D, et al: Validation studies for models projecting the risk of invasive and total breast cancer incidence. Journal of the National Cancer Institute, 91(18):1541-8. 1999.

Updated Atlas of Cancer Mortality Released. Geographic variation in cancer rates provides important clues to the role of lifestyle and other environmental factors that affect cancer risk. The NIH has published a new atlas of cancer mortality, which is available both in print and as a data-rich, searchable web site (http://www.nci.nih.gov/atlas/mortality.html). This atlas updates previous mortality maps and, for the first time, presents data specifically on African Americans. The geographic patterns displayed in the Atlas should help identify areas for further epidemiologic investigation into the causes of

cancer and assist in setting priorities for public health activities in the area of cancer prevention and control.

Atlas of Cancer Mortality in the United States:1950-1994. National Institutes of Health Publication No. 99-4564. Washington, DC: US Government Printing Office. 1999.

Update on Efforts to Develop a Vaccine for Otitis Media. Intramural scientists have developed a conjugated protein to be used as a possible vaccine against nontypeable *Haemophilus influenzae*, a leading cause of otitis media in children for which there is no vaccine available. Their studies showed that the investigational vaccine is safe and confers immunity and protection against infection in animal models. A Phase I clinical study is nearing completion that will evaluate the safety and immunogenicity of the investigational vaccine for otitis media in adult volunteers. Forty volunteers have been injected with the vaccine and 28 of them have been injected with a second dose. Only minor adverse side effects have been observed. The preliminary antibody data from the volunteers demonstrated that the vaccine was able to elicit specific antibody against the pathogen, that this investigational vaccine is safe and immunogenic in adults and, therefore, may be useful for preventing otitis media in children. A Phase II clinical study is planned to further evaluate the safety and immunogenicity of the investigational vaccine in children. [secondary – treatment]

Sun J, Chen J, Cheng Z, Robbins JB, Battey JF, Gu XX: Biological activities of antibodies elicited by lipooligosaccharide based-conjugate vaccines of nontypeable *Haemophilus influenzae* in an otitis media model. Vaccine, 18(13):1264-72. 2000.

First Fractures in Older Women and Men Should Not Be Ignored. Hip fractures among women 65 and older have increased significantly in the last decade. Older people run a higher risk of falls because they are generally more sedentary, have weaker muscles and poorer balance, and take more medication that can make them dizzy. A major thrust in osteoporosis research is to identify the subset of the population at highest risk of fracture. Researchers followed individuals who had forearm fractures between 1975 and 1994 to assess whether the forearm fracture was predictive of other fractures in the future, and determined that it was predictive. Currently, only about 5 percent of patients seeing an orthopaedic surgeon for a fracture receive any kind of followup directed toward evaluation for osteoporosis and prevention of future fractures. Forearm fractures represent a missed opportunity for followup, evaluation, and intervention in patients at relatively high risk of subsequent fractures.

Cuddihy MT, Gabriel SE, Crowson CS, O'Fallon WM, Melton LJ III: Forearm fractures as predictors of subsequent osteoporotic fractures. Osteoporosis International, 9(6):469-75. 1999.

Simplified Screening Test for Hyperlipidemia. The measurement of cholesterol in the different serum lipoprotein fractions is valuable for identifying patients that have a high risk for developing heart disease, but it requires multiple tests. A new test was developed that can be used to quantify all of the major lipid fractions, namely total-cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides.

The new test is simple to perform and relatively inexpensive and can be used as a screening test for the prevention of heart disease. [secondary – diagnosis]

Sampson ML, Csako G, Remaley AT: Dual HDL/total cholesterol test: a single-tube, homogeneous assay for sequential measurement of HDL cholesterol and total cholesterol. Annuals of Clinical Biochemistry, 37(Part 4): 479-87. 2000.

Treatment Can Reduce Negative Effects of Maternal Depression on Children's Cognitive Development. Every child deserves the very best start in life. It is especially tragic when a child does not develop to full ability as a result of a circumstance that can be mediated. Several NIH-funded studies indicate that depression in mothers can negatively affect cognitive development in their infants and toddlers. However, we know little about the effectiveness of interventions that have been developed to prevent this; clearly, it is critical that they need to be tested. The initial findings from an intervention called Toddler-Parent Psychotherapy (TPP) appear promising. TPP involves weekly interventions over a year where therapists help mothers to recognize their children's developmental stages, as well as to be aware of their own reactions and behaviors in response to the toddler's behaviors. The hope is to facilitate positive mother-child interactions. This intervention was compared to two control groups – one of depressed mothers and toddlers with usual community care, and another sample of nondepressed mothers and their toddlers. The depressed mothers and their children were randomly assigned to the treatment or control group. The study began when the children were 20 months old; all groups of toddlers had comparable scores on measures of cognitive development. Outcomes at age 3 indicated that in the group of children and mothers who received intervention, as well as in the normal control group, toddlers maintained a higher rate of cognitive development when compared to the depressed group who received standard community care. The greatest lag in development was seen among toddlers whose mothers had subsequent depressive episodes. This research is important to elucidate what is needed to intervene early in a child's environment in order to have a positive impact on his or her overall future development.

Cicchetti D, Rogosch FA, Toth S: The efficacy of toddler-parent psychotherapy for fostering cognitive development in offspring of depressed mothers. Journal of Abnormal Child Psychology, 28(2):135-48. 2000.

Newer Medications are Helping Patients with Schizophrenia Reduce their Abuse of Drugs and Alcohol. While there has been *anecdotal* evidence that the newer antipsychotic medications help reduce patients' use of illegal drugs, alcohol and cigarettes, NIH researchers have now documented that one of the new antipsychotic drugs, clozapine, has real potential for substance abuse treatment. Patients in this study who received clozapine had far fewer days abusing alcohol in a 6 month period and were far more likely to have stopped drinking than patients taking older antipsychotic drugs. Use of illegal drugs was also reduced. Because the study was naturalistic and not a controlled trial, these findings need to be explored further in randomized controlled trials. There is also a critical need for translational research exploring the neurological basis for these findings and the potential for other recently developed antipsychotics to produce similar results.

Drake RE, Xie H, McHugo GJ, Green AI: The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia. Schizophrenia Bulletin, 26(2):441-9. 2000.

Psychopathology Overlooked as Factor in Spouse Abuse. NIH research is pointing to the need to consider psychopathology as a factor in serious and chronic spouse abuse. In a study conducted with 102 abusive men and their wives with a history of violence in their marriages, three major subtypes were identified. In the first type, chronic and particularly serious spouse assaults involve men who are antisocial and violent both in the community and at home, and who also have developmental histories and characteristics associated with antisocial personality disorder and psychopathy. A second type – also involving men with a history of chronic and serious spouse assaults – consists of men with borderline personality disorder combined with symptoms of depression and anxiety. Their developmental histories also reflect this disorder. In a third type of spouse abusers, whose assaults are usually not chronic and are less serious, psychopathology is typically lacking, and situational factors may be important. Differentiating subtypes of spousal abusers based on the type and extent of psychopathology may allow more targeted interventions to protect women from repeated assault.

Waltz J, Babcock JC, Jacobson NS, Gottman JM: Testing a typology of batterers.. Journal of Consulting and Clinical Psychology, 68(4):658-69. 2000.

Nurse Home Visitation Carries Beneficial Effects for African American Mothers Too. While NIH research has shown that home visitation programs wherein nurses intervene in the home to improve maternal and child outcomes had favorable short- and long-term results, including a decrease in adolescent delinquency, it was of limited applicability since it was tested in a primarily white, semi-rural population. However, many of the short-term findings from the study of white families have been replicated with urban African American mothers at risk (unmarried, <12 years of education, or unemployed). Follow-up research continues in order to determine whether the program would continue to demonstrate effectiveness over time. A three-year follow-up of the 2-year home visitation program and the comparison control group indicated that African American women who received home visits by nurses had fewer closely spaced subsequent pregnancies, and fewer months of using Aid to Families with Dependent Children and food stamps than their counterparts in the control groups. Moreover the effects continued when the program was ended. While these results were smaller in magnitude than those achieved in a previous trial with white women living in a semi-rural setting, the direction of the effects was consistent across the two studies.

Kitzman H, Olds DL, Sidora K, et al: Enduring effects of nurse home visitation on maternal life course: a 3-year follow-up of a randomized trial. Journal of the American Medical Association, 283(15):1983-9. 2000.

Neuropsychological Functioning in HIV Patients Receiving Anti-Retroviral Therapy. Despite major advances in the treatment of HIV infection in the last decade, neurocognitive complications that affect the ability to think clearly and efficiently process information, continue to afflict many infected

individuals. To examine how antiretroviral therapy affects this cognitive function, researchers at an NIH-funded HIV Neurobehavioral Research Center are studying HIV-infected individuals with symptomatic neurocognitive impairment. In the Cognitive Intervention Trial, all subjects start a new anti-retroviral regimen at entry and are followed closely through standardized neuropsychological testing, lumbar puncture, and blood samples. Of the 17 subjects enrolled thus far, 59% improved neurocognitively after 12 weeks of antiretroviral therapy. The degree of improvement was found to correlate with restoration of immune function (measured as blood CD4+ lymphocytes) and reduction of HIV replication below detectable levels (measured as HIV RNA) in cerebrospinal fluid (CSF), but not blood. These findings support the theories that HIV RNA levels in CSF reflect those in the brain in cognitively impaired individuals, and that antiretroviral therapy is efficacious in the nervous system of most, but not all, patients.

Letendre SL, Lanier ER, McCutchan JA: Cerebrospinal fluid ß chemokine concentrations in neurocognitively impaired individuals infected with human immunodeficiency virus type 1. Journal of Infectious Diseases, 180(2): 310-9. 1999.

Markedly Elevated HIV, Hepatitis C Prevalence in Those with Serious Mental Illness. Hepatitis C virus (HCV) is the most common chronic blood-borne infection in the U.S. and is transmitted through the same routes as HIV. Although increased prevalence of HIV in persons with serious mental illness has been noted for nearly a decade, the prevalence of HCV had not been studied in this population. A recent survey of 1,000 persons with serious mental illness indicated the prevalence of HIV to be 8 times the U.S. population rate, and the prevalence rate of HCV to be 11 times the U.S. population rate. Substance use disorder, use of injection drugs, snorting drugs, and use of crack cocaine were associated with the higher rate of infection. Because those infected with HCV may be asymptomatic for decades, they commonly fail to receive appropriate treatment to limit liver damage, and may unknowingly be a source of infection to others. These data compel further development of prevention, screening, and treatment for both HIV and HCV among persons with serious mental illness, particularly those with co-existing substance-use disorders.

Rosenberg SD, Goodman LA, Osher FC, et al: Prevalence of HIV, hepatitis b and hepatitis c in people with severe mental illness. American Journal of Public Health, 91(1):1-7. 2000.

New Insights into Prejudice Reduction. It has long been believed that simple categorization of people into different ethnic and social groups led to the development of stereotypes and hostile relations between those groups. Accordingly prejudice reduction focused on de-emphasizing social categories in order to achieve more harmonious intergroup relations. NIH-supported scientists, however, have recently shown that categorization may in fact have the opposite effect. A "diversity appreciation" intervention – a message advocating a multicultural ideology – can lead to prejudice reduction even while increasing the recognition of cultural and ethnic differences. While these findings are still preliminary, the emphasizing of social category differences that may lead to greater positivity toward minority group members can have important implications for their well-being.

Wolsko C, Park B, Judd CM, Wittenbrink B: Framing interethnic ideology: effects of multicultural and color-blind perspectives on judgments of groups and individuals. Journal of Personality & Social Psychology, 78(4):635-54. 2000.

Identification of Genetic Risk Factors that Affect Occurrence of Oral Cancers in African-Americans. Oral cancer is, to a great extent, a tobacco-related disease that affects African-American men at a significantly higher incidence than Caucasian men. Genetic polymorphisms are associated with a number of genes that code for enzymes involved in the metabolic detoxification of tobacco carcinogens. Included in these enzymes are the glutathione S-transferases (GSTs). The potential role of the absence of one of the GSTs and a polymorphism in a second GST were examined in African-American and Caucasian patients with histologically confirmed primary oral cancer. The association of the absence of the one enzyme in African-Americans with oral cancer was the strongest in heavy smokers. Interestingly, no significant associations were observed between these genotypes and oral cancer risk in Caucasians. Thus, the results indicate that these genotypes play important roles in risk for oral cancer among African-Americans and implicate these enzymes as important tobacco carcinogen detoxifying enzymes in this population. Consequently, these polymorphisms could be used for screening African-Americans for risk of oral cancers.

Park LY, Muscat JE, Kaur T, et al: Comparison of *GSTM* polymorphisms and risk for oral cancer between african-americans and caucasians. Pharmacogenetics, 10(2):123-31. 2000.

Osteoarthritis More Prevalent in Younger Groups of Middle-Aged African-American and Caucasian Women than Expected. Since osteoarthritis (OA) has been considered a disease of the elderly, few population-based studies have examined OA frequency and characteristics in individuals under age 45. A recent study in more than 1,000 women 28-52 years of age found that OA of the hand and knee detected by x-ray is common in women after the age of 40, and the emergence of OA occurs rapidly between 35 and 40 years for both African-American and Caucasian women. Knee OA was much more frequent in African-American women (23.1%) compared with white women (8.5%) of the same age, even after adjusting for age, body size, and history of joint injury. The frequency of hand OA was more comparable between African American (25.5%) and white women (19.2%). This study provides strong evidence that primary prevention of OA should be attempted in young adulthood. The striking difference in prevalence of knee OA between African-American and white women in this study highlights the need to identify additional factors affecting the risk for developing OA.

Sowers M, Lachance L, Hochberg M, Jamadar D: Radiographically-defined osteoarthritis of the hand and knee in young and middle-aged african american and caucasian women. Osteoarthritis and Cartilage, 8(2):69-77. 2000.

Exercise Stress Testing May Not Be Needed for Older Persons Beginning an Exercise Program. While the benefits of physical activity and exercise among older persons are becoming increasingly clear, the role of exercise stress testing and safety monitoring for older persons who want to

start an exercise program is unclear. Further, current guidelines for routine exercise stress testing may deter older persons from beginning an exercise program, either because of the cost of testing, or because they infer from the guidelines that exercise poses higher risks than it actually does. NIH-funded investigators suggest in a new study that the benefits of exercise for the elderly, balanced against the fairly minor increase in risks they estimate, may be sufficient to encourage the initiation of an exercise program for most older persons without a prior exercise stress test.

Gill TM, DiPietro L, Krumholz HM: Role of exercise stress testing and safety monitoring for older persons starting an exercise program. The Journal of the American Medical Association, 284(3):342-9. 2000.

Commonly Prescribed Diuretic Protects Against Osteoporosis. The lifetime risk of osteoporotic fracture in the U.S. is 40% in women and 13% in men. Because age-related bone loss increases susceptibility to fracture, strategies aimed at preserving bone mass are important in preventing fractures and preserving independence in older individuals. Large observational studies have consistently shown that use of thiazide diuretics, usually prescribed to treat high blood pressure, is associated with higher bone density and about a 30% lower risk of hip fracture. NIH-funded investigators recently completed a randomized, controlled clinical trial to test the effect of thiazides on bone density in older men and women with normal blood pressure. Among healthy older adults, low-dose hydrochlorothiazide did preserve bone density at the hip and spine. The modest effects observed over three years, if accumulated over 10-20 years, may explain the 1/3 reduction in hip fracture risk associated with thiazides in many epidemiologic studies. The results of this trial suggest that low-dose thiazide therapy may have a role in strategies to prevent osteoporosis.

LaCroix AZ, Ott SM, Ichikawa L, Scholes D, Barlow WE: Low dose hydrochlorothiazide and preservation of bone density in older adults: a randomized, double-blind, placebo-controlled trial. Annals of Internal Medicine, 133(7): 516-26. 2000.

Highly Reduced Protection Against *Streptococcus Pneumoniae* after Deletion of a Single Heavy Chain Gene in Mouse. *Streptococcus pneumoniae* (SPn) infections are responsible for many deaths each year in the United States, mostly among the aged, but also in young children and immune deficient patients. These highly susceptible human populations are least responsive to immunization with the currently available vaccine. A vaccine using phosphocholine (PC), a component of the SPn bacterial wall, conjugated to immunogenic protein carriers successfully provided protection against SPn in both normal and immunodeficient mice. Researchers recently discovered that by deleting a single gene in mice, they could greatly reduce the protection provided by these PC-based vaccines, indicating that this gene is a critical element in the production of protective antibodies. A greater understanding of the immunogenicity and molecular dynamics of anti-PC responses may provide valuable information into the generation of clinical vaccines against SPn.

Mi QS, Zhou L, Schulze DH, et al: Highly reduced protection against *Streptococcus pneumoniae* after deletion of a single heavy chain gene in mouse. Proceedings of the National Academy of Sciences, 97(11):6031-6. 2000.

Exercise as a Fall Prevention Program for Elderly Individuals. Falls occur at the rate of about 1.5 falls per nursing home bed per year. The consequences of falls among nursing home residents are serious, including fractures, soft tissue injury and fear of falling again. Even for community-residing older adults, the fear of falling may compromise their quality of life and independence. A small study in two nursing homes explored an exercise intervention in preventing falls among residents. An ankle strengthening and walking program was evaluated in terms of improvements in balance, ankle strength, walking speed, falls and fear of falling. The evaluations at three months after completion of the program were maintain or improved. The researcher currently is extending the study to a larger number of nursing homes in order to further test the intervention.

Schoenfelder DP: A fall prevention program for elderly individuals. Journal of Gerontological Nursing, 26(3):43-51. 2000.

Cardiovascular Disease Risk Factors in Young Diabetics. In adults, insulin-dependent diabetes mellitus is a risk factor for hardening of the blood vessels and heart disease. A new study reports that children with diabetes also are at risk for high blood levels of cholesterol. Cholesterol is rarely measured in this young population. Targeting cholesterol screening only to those who have a family history of high cholesterol is not supported by the study, since having a negative family history of heart disease did not predict total cholesterol. Researchers concluded that, in addition to achieving good blood sugar control, young diabetic patients need to have assessments of cholesterol. Also, exercise and blood sugar control may be most beneficial for those at greatest risk of heart disease as indicated by their total cholesterol.

Lipman TH, Hayman LL, Fabian CV, et al: Risk factors for cardiovascular disease in children with type 1 diabetes. Nursing Research, 49(3):160-6. 2000.

Health Choices of Postpartum Mothers. Following a baby's birth, a mother faces changes and choices in her patterns of work, sleep, nutrition, and exercise. Nurse investigators examined behaviors of 124 relatively high-risk mothers, most of whom were African American, poor, and unmarried. Half of the women in the study delivered preterm infants. Data on maternal weight, nutrition, exercise, sleep, caffeine intake and smoking collected at birth and 1, 2, and 4 months showed no differences between the mothers of preterm babies and those with full-term infants. Women in both groups lost weight by decreasing carbohydrate consumption, but dietary fat increased and exceeded USDA recommendations as mothers skipped meals and ate high-fat snacks and fast food. Exercise increased but remained insufficient to contribute to weight loss, vitality, or psychological health. By the fourth month, mothers were getting 7 hours of sleep per night and did not use caffeine to increase alertness. However, the number of women who smoked increased at each data point, rising from 19% of women at the time of

delivery to 29% by four months after the baby was born. The study highlights specific areas in which mothers need help in making choices that can benefit themselves and their children.

Gennaro S, Fehder W: Health behaviors in postpartum women. Family and Community Health, 22(4):16-26. 2000.

Leptin's Role in Women's Weight Loss. The hormone leptin plays an important role in controlling body weight by regulating both energy intake and expenditure. Leptin concentrations increase with obesity and tend to decrease with weight loss. Nurse researchers have examined which physical factors are related to changes in leptin concentrations following weight loss in obese, postmenopausal women. Their results suggest that changes in leptin with weight loss can be predicted by baseline hormonal levels as well as other physical factors in obese, postmenopausal women. These findings are significant for further understanding the relationships between hormonal changes and body weight control.

van Rossum EFC, Nicklas BJ, Dennis KE, Berman DM, Goldberg AP: Leptin responses to weight loss in postmenopausal women: relationship to sex-hormone binding globulin and visceral obesity. Obesity Research, 8(1):29-35. 2000.

Smoking Cessation Reduces Risk of Cataract. Cataract is a major medical and public health problem. It is a leading cause of visual impairment and costs associated with cataract extraction are millions of dollars annually in the United States. Smokers are known to be at increased risk of developing cataracts. A large prospective epidemiologic study following a group of almost 21,000 male physicians for 14 years has determined that smoking cessation reduces the risk of cataract. At least part of this decreased risk is due to less lifetime cigarette usage, although the investigators provide evidence to suggest that some smoking-related damage to the lens of the eye is reversible. These findings provide additional evidence of the benefits derived from smoking cessation.

Christen WG, Glynn RJ, Ajani UA, et al: Smoking cessation and risk of age-related cataract in men. Journal of the American Medical Association, 284(6):713-6. 2000.

New Light on the Mechanism of Autoimmunity. Autoimmunity is a major pathogenic mechanism of inflammatory diseases in the eye and other organs. In the normal individual, autoimmunity is prevented by development of immunotolerance to self antigens, while abrogation of tolerance triggers autoimmunity. Not much is known about the processes by which tolerance is abrogated. New knowledge on this topic was produced in a recent study at the NIH, showing that the physiologic process of tolerance development toward a self protein is abrogated when antibody to this protein is present on a type of lymphocytes designated "B-cells." The new information may be helpful for development of new measures to prevent/reduce development of pathogenic autoimmunity.

de Vos AF, Fukushima A, Lobanoff MC, et al: Breakdown of tolerance to a neo-self antigen in double transgenic mice in which B cells present the antigen. The Journal of Immunology, 164(9):4594-4600. 2000.

New Insights into Retinal Damage Triggered by Infection. The manner in which the host responds to an insult, such as an infection, will contribute, in part, to ocular tissue damage. It is estimated that the protozoan parasite, *Toxoplasma gondii*, infects 500 million humans worldwide. This organism is also the most frequently identified cause of ocular inflammation, and the retinal damage is an important initiator of blindness in young adults. Scientists at the NIH demonstrated in cell culture experiments that *T. gondii* infection of critical retinal pigment epithelial cells can induce gene expression and secretion of molecules that contribute to the damage of ocular tissues. These findings identify key molecules produced by retinal cells in response to infection and suggest novel interventive strategies to prevent retinal tissue damage.

Nagineni CN, Detrick B, Hooks JJ: *Toxoplasma gondii* infection induces gene expression and secretion of 1(IL-l), IL-6, granulocyte-macrophage colony-stimulating factor, and intercellular adhesion molecule 1 by human retinal pigment epithelial cells. Infection and Immunity, 68(1):407-10. 2000.

Autoimmunity and the Eye. To avoid potentially vision-damaging effects of the inflammatory response, the eye responds to pathogens by suppressing immunity. In the anterior portion of the eye, this reaction is known as Anterior Chamber-Associated Immune Deviation (ACAID). ACAID is a form of immune tolerance, the ability to recognize self. Loss of this ability results in autoimmune disease. Scientists have recently worked out the steps involved in the ACAID response. ACAID appears to involve specialized lymphocytic cells, Natural Killer T cells (NKT), raising the possibility that these cells regulate the determination of self from non-self. These findings suggest that NKT cells could be modified for prevention and therapy.

Sonoda KH, Exley M, Snapper S, Balk SP, Stein-Streilein J: CD1-reactive natural killer T cells are required for development of systemic tolerance through an immune-privileged site. Journal of Experimental Medicine, 190(9): 1215-25. 1999.

Hong S, Kaer LV: Immune privilege: Keeping an eye on natural killer T cells. Journal of Experimental Medicine, 190(9):1197-1200. 1999.

Risk of HIV Infection Associated with Sexually Transmitted Diseases. Studies have shown an association between people having sexually transmitted diseases (STDs) that cause genital ulcers or discharge and an increased risk of their becoming infected with HIV. In a clinical trial in Uganda, NIH investigators sought to determine whether the association is causal or coincidental and, if causal, to what extent STDs, as a co-factor, increase the rate of HIV infection. The larger aim was estimate the extent to which universal STD treatment programs might lower HIV infection rates. The investigators' findings indicate STD treatment strategies are unlikely to substantially reduce the numbers of people who get HIV in populations where many people already have the disease. However, the findings do indicate that, for individuals, STDs increase the risk of getting an HIV infection and of transmitting HIV to sexual partners.

Gray RH, Wawer MJ, Sewankambo NK, et al: Relative risks and population attributable fraction of incident hiv associated with symptoms of sexually transmitted diseases and treatable symptomatic sexually transmitted diseases in rakai district, uganda. AIDS, 13(15):2113-23. 2000.

HIV Levels in Female Genital Secretions Strongly Correlate with Levels in Plasma. Transmission of HIV from women to men and from women to infants is strongly associated with the amount of virus (viral load) in the woman's blood. Researchers have demonstrated that the levels of HIV found in a woman's genital secretions strongly correlate with the levels of HIV detected in their blood plasma. Reductions in HIV levels in the genital tracts of women could have a significant impact on the transmission of HIV.

Kovacs A, Chan LS, Chen ZC, et al: HIV-1 RNA in plasma and genital tract secretions in women infected with HIV-1. Journal of Acquired Immune Deficiency Syndrome, 22(2):124-31. 1999.

Estimating Absorption of Iron from Common Foods Eaten in China. Iron deficiency anemia continues to be one of the leading nutritional disorders in China, affecting hundreds of millions of adults, despite an average iron intake greater than two times the U.S. Recommended Dietary Allowance. The authors developed an equation to estimate bioavailability of dietary non-heme iron and predict iron status by correcting for the dietary intake of enhancers (ascorbic acid, animal food sources, and vegetables and fruits) and inhibitors (rice, beans, and tea). The new method will be useful to refine population based assessments of nutritional anemia and guide public health interventions in China.

Du S, Zhai F, Wang Y, Popkin BM: Current methods for estimating dietary iron bioavailability do not work in China. Journal of Nutrition, 130(2):193-8. 2000.

Diversity of HIV type 1 in Senegal. It is well established that several subtypes of HIV-1 viruses exist, yet little is known about the extent to which individual subtypes of the virus change genetically over time. American and Senegalese scientists analyzed subtype A of the HIV-1 virus in Senegal over a ten year period. They have found that the genetic diversity doubled during this period. This finding suggests that the effectiveness of HIV vaccines directed against individual subtypes, once vaccines become available, will be increased on a population basis if they are administered at the beginning of an epidemic and before the virus changes its genetic pattern significantly.

Sankale JL, Hamel D, Woolsey A, et al: Molecular evolution of human immunodeficiency virus type 1 subtype A in senegal: 1988-1997. Journal of Human Virology, 3(3):157-64. 2000.

Multivitamin Supplements to Pregnant Women Improve Birth Weight but do not Reduce Transmission of HIV Infection Poor nutritional status among HIV-infected women is associated with greater mother-to-child transmission of HIV infection. This study, involving scientists from Tanzania and the United States, was designed to test whether simple and inexpensive nutritional

supplements, multivitamins and/or vitamin A, would reduce such transmission rates. Whereas no effect of either multivitamins or vitamin A on transmission was found, there was a significant reduction in low birth weight among mothers receiving multivitamins. This effect was limited to babies born of HIV-negative mothers, and thus appears to be a useful public health tool to improve pregnancy outcomes and early infancy survival.

Fawzi WW, Msamanga G, Hunter D, et al: Randomized trail of vitamin supplements in relation to vertical transmission of HIV-1 in tanzania. Journal of Acquired Immune Deficiency Syndrome, 23(3):246-54. 2000.

STORIES OF DISCOVERY

Heart Disease and History – A Good Cholesterol Story

On his voyage of exploration to the New World in the early 1600s, Captain John Smith discovered a number of tiny islands off the Virginia shore in the Chesapeake Bay. Today, four centuries later, one of them has found a place in the annals of modern American medicine. Tangier Island was first settled in 1686 by John Crockett and his eight sons. Later, others with English and Welsh backgrounds came to live there and, isolated from the mainland, they intermarried for many generations. Despite harsh weather and epidemics of Asian cholera, tuberculosis, measles, and smallpox, the descendants of these families are to be found on Tangier Island to this day. And hidden among the genes of some of these descendants lurks a mutation of extraordinary importance.

Tangier disease was discovered some 40 years ago by Donald Frederickson, who later became a director of the NIH. Affected individuals are unable to process cholesterol appropriately, due to a genetic defect that reduces "good" blood cholesterol – HDL – to a bare minimum. As a result, in addition to their unusual orange tonsils, individuals with Tangier Disease have persistently high levels of "bad" blood cholesterol – LDL – and suffer from premature coronary heart disease. This genetic legacy brought by the settlers of Tangier Island centuries ago has become today a key to understanding the major modern threat to the health of Americans.

The powerful role in heart disease of cholesterol and its transport molecules, called lipoproteins, had been becoming clear about the same time that Frederickson discovered Tangier Disease. In a 1949 meeting of the Faraday Society, the separation of lipoproteins into two classes – alpha and beta, later to become known as HDL and LDL – had already been celebrated. This success stimulated a surge of interest among scientists bent on understanding the full picture of cholesterol metabolism.

Indeed, by 1951 it was clear that low levels of HDL were associated with a tendency to develop coronary heart disease. At the same time, LDL was perceived to be the culprit in the mismanagement of cholesterol processing, leading somehow to atherosclerosis. The protective effect of HDL was fully confirmed in the late 1950s by findings from the Framingham Heart Study. That study continues to this day to acquire information about the risks of heart disease experienced by the original group of volunteers from Framingham, Massachusetts, and their offspring.

In the 1960s and 1970s, researchers were able to describe five separate conditions characterized by high blood cholesterol that involve abnormalities in the lipoproteins. The discovery of how LDL cholesterol is cleared from the blood, which brought the Nobel prize to Michael Brown and Joseph Goldstein, then set the stage for new and more effective treatments for patients with these conditions. Family and twin studies followed, and it soon became established that, at least in part, HDL deficiency was under genetic control; clearly, a search for the actual genes involved would be expected to pay off handsomely.

As the science of molecular genetics has progressed quickly in recent years, driven by the quest to describe the whole human genome, many new disease-related genes have been discovered. One of them, the so-called ABC-1 gene, found on human chromosome 22, has now been shown to be the very one involved in Tangier Disease. The gene appears to be intimately involved in HDL deficiency and is pivotal to the disease process in which cholesterol is inadequately cleared from the blood.

Now that this mechanism has been uncovered, completely new ways of preventing and controlling coronary heart disease begin to present themselves. Until now, most strategies involving cholesterol have emphasized the reduction of LDL. Approaches may now emerge that emphasize the flip side of the coin – attempts to raise HDL. And the prospect of using modern tools of molecular medicine, such as gene therapy, may now become feasible based on identifying and mapping genes such as ABC-1.

The world around Tangier Island in the year 2000 is fast changing to keep pace with modern society, but the ABC-1 gene stands as a permanent reminder that human diversity and human ingenuity can combine the old with the best of the new, for the benefit of all.

1930's Mystery Solved with Modern Day Technologies: New Prevention Principle Unveiled

What was one of the great mysteries of the prevention research world in the 1930s has been brought to new light with 1990s technology and knowledge. The "Cambridge-Somerville" intervention mystery of the 1930s was finally solved when researchers in the 1990s equipped with videocassettes, sophisticated coding schemas, and other state-of-the art equipment, began to understand why a modern day intervention program that was based on established prevention principles was also showing negative results. The "Cambridge-Somerville" study was designed to counteract the negative influences on boys growing up in high crime neighborhoods. The intensive, individually tailored intervention that involved family support lasted 5½ years and even by today's high standards, would be considered cutting edge. However, despite the excellent study and program design, the results of a 30-year follow-up evaluation showed the surprising outcome that the intervention actually produced more negative, outcomes (such as a higher prevalence of individuals who were convicted of crime, diagnosed with alcoholism, schizophrenia, or manic depression) in those who received the intervention then those who did not. Also, the greatest negative effects were found with those individuals who were most engaged in the program, another completely unexpected, certainly counter-intuitive result.

Similarly, researchers were completely baffled when the modern day Adolescent Transitions Project in Oregon, a comprehensive school-based prevention program with a very strong parent component, showed negative outcomes for the high-risk youth who engaged in the intervention versus the comparison groups who did not. Researchers had to ask themselves *why* this was happening. It seemed like they were doing everything right. They were tailoring the program to the needs of the middle and junior school students, they were actively engaging parents in the programs, yet the results were showing that some teens who participated in the intervention used tobacco more frequently, and were rated by teachers as more delinquent than the teens who did not participate in the program. They also found that older youth with the highest initial levels of problem behavior were most susceptible to the negative effect.

To investigate this further, scientists examined the results from other research at the Oregon Social Learning Center, including a study that was researching anti-social behavior in boys by videotaping their interactions with peers. These videotapes revealed a sequence of interactions researchers termed "deviancy training." They observed that teens were inadvertently being positively encouraged through smiles and laughter when references were being made to deviant behavior. Further, when both boys in the pair were characterized as antisocial, almost all positive reactions were to deviant talk. On the other hand, less deviant adolescents often ignored or failed to reward such talk. Researchers began seeing a pattern, they began to suspect that how students were grouped in programs had an effect on the results of the study.

In follow-up research, the intervention was modified to address the problem of deviancy training. Researchers ensured that the groups were carefully supervised to discourage this direct encouragement of problem behavior. Yet, despite the supervision, grouping these boys again resulted in negative effects.

Videotapes of the intervention sessions further suggested that age might be an additional factor of importance. Older boys, and more physically mature boys, seemed to be able to mobilize more group attention more effectively than younger, less deviant boys. Moreover, attention may have come less from the content of discussions and more from dress, behavior, and nonverbal expressions.

These studies have taught us an important lesson – youth at high risk should not be grouped together because it can worsen problem behaviors including those behaviors related to school and drug use. Realizing this principle, researchers then began to look at research from past studies for similarities with negative effects, including the Cambridge-Somerville intervention.

Researchers realized that the same grouping phenomenon had occurred in that study as well, thus ending the 60-plus year mystery. Moreover, these findings have led to the development of new analytic techniques and observational methods that have produced a better understanding of why the negative effects occurred and what prevention designers can do to protect against them. Determining that youth at high risk for behavior problems should not be placed in prevention programs with other high risk youth is one of the new prevention principles that NIH-researchers have unveiled. This revelation has implications far beyond the drug abuse community. This is a finding that is relevant to other disciplines as well, including clinical and correctional settings.

Reducing Mother-to-Child HIV Transmission in Less Developed Countries

Ten years ago, infants born to human immunodeficiency virus (HIV)-infected women had a significant risk of entering the world infected with the HIV virus. At that time, the medical community knew of only one way to reduce mother-to-child HIV transmission: avoid breast feeding. In more developed countries, about one in every four HIV-infected women transmitted the infection to their children; in less developed countries where most women breastfeed, transmission rates were as high as 40 percent. Then, in the mid-1990s, the results from a series of clinical trials sponsored by the NIH began to demonstrate other effective ways to prevent mothers from passing the AIDS virus on to their children.

The first breakthrough came in 1994 with the announcement of a remarkable advance. Scientists reported a nearly 70 percent reduction in mother-to-child HIV transmission after giving zidovudine to the mother during pregnancy and labor, and to the newborn infant for six weeks following birth. By incorporating this regimen into clinical practice in the U.S. and in other developed countries, physicians cut the rate of mother-to-child transmission to as little as 4-6 percent. In the span of a few years, this practice has dramatically reduced perinatal AIDS cases in the U.S. by 86 percent for infants under 1 year and by 78 percent for children 1 to 5 years old. Scientists further discovered that elective cesarean delivery, in addition to using zidovudine, could further reduce transmission rates to 2 percent or less.

However, although researchers knew that various factors contribute to perinatal HIV transmission, they did not know which, if any, was the most important. After examining the results of a number of studies, scientists concluded that the amount of virus in a mother's blood is the critical factor for passing HIV on to her infant. Thus, by reducing HIV viral levels in women during pregnancy, scientists had discovered yet another very important tool to reduce the risk of mother-to-infant transmission.

This extraordinary success in more developed countries, however, stands in stark contrast to the continuing perinatal epidemic in less developed countries. A major barrier to reducing mother-to-child transmission in less developed regions of the world is the cost of the drugs, although the U.S. Government and pharmaceutical companies have taken steps to make anti-HIV drugs more affordable. The widespread practice of breastfeeding, the lack of a strong public health network in some parts of the world, and the complexity and expense of drug regimens all make it difficult to reduce transmission of this disease that threatens the future of entire nations.

Undaunted, scientists, clinicians and public health workers have continued working to remove barriers to quell the growing epidemic in the developing world. For example, working with the host countries, researchers designed clinical trials that could scientifically demonstrate how lower-cost and shorter regimens of antiretroviral drugs could effectively help to prevent the spread of HIV in less developed countries. However, the trials raised ethical questions concerning the use of anything short of the "standard known treatments" in developing countries. On the one hand, many scientists believed that it was ethical to test regimens that could be feasibly implemented in developing countries, even if these

regimens fell short of the standard known treatment. Other scientists believed that clinical trials should use only the standard known treatments, even if it was unlikely that these treatments could be administered routinely in developing countries. Despite the debate, the research has continued with the goal of developing sustainable therapies for worldwide applications; and the efforts are paying off.

Recently, NIH-supported scientists made a major stride toward this goal: they offered developing countries hope by demonstrating that several short, simple, and less expensive antiretroviral regimens could reduce mother-to-child HIV transmission. First, women who were given zidovudine during their last month of pregnancy and during labor reduced the risk of transmitting HIV to their infants by 50 percent if they did not breast feed, and by 38 percent if they did. Fortified by their significant success, researchers went on to show that a single dose of nevirapine, given once to the mother at the onset of labor and once to her child at 48 hours of age, reduced transmission by 47 percent when compared to the short regimen of zidovudine. The reduced cost of nevirapine, combined with its simpler treatment schedule, makes it one of the few deliverable and sustainable strategies for preventing HIV infection in resource-poor settings.

Given foresight and perseverance, NIH-supported scientists have enabled the developing world to prevent HIV-1 infection in over 250,000 children born each year to HIV-infected mothers.

Investing in the Community Can Improve Outcomes for Infants

The World Health Organization estimates that 6.9 babies per one thousand born in the United States will die before their first birthday. The U.S. ranks 25th among industrialized nations in infant mortality. One factor closely associated with infant death is low birth weight (less than 5.5 pounds). The percentage of low birth weight infants has risen slowly each year since the mid-1980s. Very low birth weight infants (less than 3.3 pounds) are at greatest risk of death, experience costly interventions that disrupt family life, and experience poor long term outcomes such as cerebral palsy, autism, mental retardation, vision/hearing impairments and other developmental disabilities. The number of very low birth weight infants has also been steadily increasing. The rates of low birth weight are higher in adolescents and twice as high among African American women; other minority groups also experience high rates of low birth weight and preterm births.

Early findings from an NIH-funded series of studies using a telephone intervention with pregnant women reduced both low birth weight rates and the incidence of preterm birth rates. An important feature of the research funded by NIH is that findings were adopted successfully by the community where the research was conducted, and incorporated into the community after the research funding period was completed.

In the early 1990's, NIH funded a randomized clinical intervention trial targeted at preventing delivery of low birth weight and preterm infants in low-income pregnant women who were considered to be high risk. The intervention used telephone calls from a registered nurse once or twice per week to assess signs of preterm labor and discuss health behaviors such as nutrition and smoking, as well as other topics of concern to the mothers. The intervention decreased the incidence of low birth weight infants in a sample of over 1500 low income pregnant women from 14% to less than 11%. More dramatic was the reduction in preterm birth rates from 15.4% to 8.7% in a subgroup of low-income African-American women who were 19 years of age and older. The cost of the intervention was approximately $117 per pregnancy. In the latter subgroup, the estimated cost savings for averting preterm births was $277 per woman and for averting low birth weight births was $92 per woman. Of note was the ability of the investigators to recruit into the study and retain over 14 weeks such as large sample of economically disadvantaged women. The investigators summarized their successful strategies in a 1997 publication.

While the study's findings were of immediate interest to a wide audience of practitioners and program planners, the investigator realized the importance of continuing the intervention in this high-risk community beyond the end of the study. Four programs utilizing the research findings were developed as the research intervention was incorporated into practice within the community. The Good Health Program was implemented at the original clinic for low-income women where the research began and was refined by having nurses designated specifically for telephone intervention. Later, a Spanish-speaking peer counselor was hired to respond to a growing proportion of clinic patients who were Hispanic. Impressed with the cost savings and reduced morbidity and mortality figures, the clinic's

parent organization, a community health center, began to move toward assuming responsibility for costs and operation of what had been the original research intervention funded by NIH.

Further implementation of the research findings expanded to an insured population of generally highly motivated women who were from a higher socioeconomic background than was the original study population. A health maintenance organization initiated Baby Watch for every pregnant woman at first contact with the HMO and developed a plan of care based on the individual's needs. A second assessment was made by the Baby Watch program at around the sixth month of pregnancy to identify concerns and provide additional information as appropriate.

In a third implementation site, state funding provided a telephone-based Parent Line for parents of children between birth and five years. Nurses provide telephone calls every two to four weeks or more frequently when needed, and parents can call a nurse six days a week from 8 a.m. to 10 p.m. For those without telephones, or whose telephone service has been temporarily interrupted, the initiative provides peer counselor home visits. Participants in the community programs in general were more likely to obtain well-child health care visits, their children were more likely to obtain age-appropriate immunizations, and more likely to breast feed.

The impact of these privately or publicly funded programs within the community paved the way for a telephone volunteer monitoring program. African-American women volunteer to give one-to-one support to African-American pregnant women. The volunteers are trained and provide at least one phone call per week to the pregnant women. The program, called Special Friends, seems to be as effective as the original research study in helping the pregnant women reduce smoking during their pregnancies.

The investigators attribute the successful adaptations of the study intervention to educating the community about the methods and findings of the original research and by working with the community to make appropriate modifications for each site. By working together, researchers and community-health nurses can integrate research findings into community-health nursing practice. This investigative team is continuing their study of community-based telephone interventions in various populations such as United States military personnel.

Amount of HIV in the Blood is the Main Predictor of Virus Transmission Among Heterosexuals

When AIDS was first recognized in 1981, patients with the disease were expected to live only 1 or 2 years. Advances in understanding HIV and how it causes AIDS have enabled scientists to develop an effective arsenal of drugs and treatment regimens. Particularly potent drug combinations known as highly active antiretroviral therapy (HAART), widely used in the United States and other developed countries, can now keep virus multiplication in check and have led to a substantial decline in HIV-related deaths. Today, many people live longer and healthier lives than was the case even a few years ago.

Although HAART's main purpose has been to improve the health of individual patients by reducing the level of HIV in the body and thereby minimizing damage to the immune system, public health officials have begun to look at antiretroviral therapy as a tool to control the spread of AIDS between infected and uninfected individuals. In other words, by using the regimen to reduce the amount of infectious virus in the blood (known as viral load), they hope to prevent or reduce the likelihood of HIV transmission from one person to another.

The concept is supported by earlier studies of mothers and their newborns, which have shown that the higher the HIV load in the mother, the more likely it is that the baby will be infected at birth. Also supporting the concept are data from NIH-funded researchers who discovered that the inexpensive antiretroviral drug nevirapine (NVP) reduced the transmission rate by half when one dose was given to an HIV-infected woman in labor and another dose was given to her baby within 3 days of birth.

Now, NIH-supported scientists have shown a direct correlation between the level of HIV in the blood and the rate of transmission of HIV through heterosexual sex, and that there appears to be a threshold below which transmission is virtually nonexistent. This discovery is the result of a large retrospective data analysis examining the link between viral load and other risk factors for heterosexual transmission of HIV. With every ten-fold rise in the concentration of HIV in the bloodstream, risk of transmission more than doubled. That is, the more virus particles individuals carried, the more likely their sexual partners were to become infected. Conversely, no one who had fewer than 1,500 copies of HIV RNA per milliliter of blood transmitted the virus to his or her partner.

This important finding provides the strongest support yet for the possibility of control of the spread of the HIV epidemic by a variety of approaches aimed at reducing infectiousness. Thus, the finding points to the need to identify and develop low-cost and feasible methods for reducing viral load for use in countries where the epidemic continues to escalate and where heterosexual transmission remains the predominant means of spreading the virus. Strategies to lower viral load include drug therapy with antiretroviral agents and vaccines.

Novel Approaches to Vaccination Could Broaden Efficacy, Spare the Needle, and be Easier to Store and Administer

Since their deployment as a key public health tool, vaccines have accomplished enormous progress in the fight against infectious diseases. Vaccines have eliminated smallpox, relegated polio to near extinction, and protected hundreds of millions people from the devastating effects of typhus, measles, pertussis, diphtheria, tetanus, hepatitis B, *Haemophilus influenzae* type b, and other infections. Using the latest molecular discoveries in immunology, microbiology, and biotechnology, NIH scientists are developing exciting new methods to deliver vaccines more effectively and easily, especially in developing countries that do not have the capacity to appropriately store and distribute current vaccine formulations. These novel vaccine delivery approaches are being applied to measles, flu, and the Norwalk virus, three viruses that cause debilitating and often fatal diseases.

DNA Vaccine. Although measles infections have been reduced substantially in industrialized nations through the use of a live attenuated (weakened) measles vaccine, the disease remains a principal cause of death among children, especially young infants, in developing countries. Immunizing very young infants against measles could significantly reduce the 1 million child deaths due to measles worldwide each year, a third of which occur among infants.

The current measles vaccine, used since the early 1960s, is not effective in children younger than 12 months of age because infants carry antibodies from their mothers that can neutralize the vaccine. Attempts to overcome the resistance of young infants to immunization, by using a vaccine 100 to 1,000 times more concentrated than usual, have been unsuccessful. Because of an increased risk of adverse effects associated with the concentrated vaccine, that strategy has been abandoned.

To overcome those problems, NIH-supported scientists have created alternative vaccines out of measles virus components such as genetic material (DNA). DNA vaccines are inexpensive to produce, chemically stable, and could have fewer side effects, particularly in the immature immune systems of very young infants. While DNA vaccines have been shown to protect mice against disease (e.g., measles, to which the mice have been exposed during an experiment) until now DNA vaccines have not been shown to be broadly effective in laboratory monkeys or in people. Recently, however, scientists from the University of Maryland Medical Center and the Johns Hopkins School of Public Health showed, in rhesus monkeys, that two experimental DNA vaccines were safe, elicited strong antibody responses, and prevented the animals from getting sick when they were exposed to measles virus. One of the experimental DNA vaccines encodes for the measles virus H glycoprotein and the other encodes the F glycoprotein. (Glycoproteins are carbohydrate/protein compounds.) Those two virus components were chosen as targets because of their known ability to induce neutralizing antibodies that disarm the measles virus. The implications of this discovery offer hope for reducing infant deaths from measles around the world. To ensure that this important work moves forward the Gates Foundation has awarded $40 million to the investigators to continue their work developing a measles vaccine for infants.

Nasal Spray Vaccine. Throughout human history, the respiratory illness influenza, "flu," has remained a major killer. In recent times, public health immunization campaigns have dramatically reduced the annual morbidity and mortality associated with the flu. However, even though most people recover from influenza, the illness still can be deadly, particularly in vulnerable populations such as the elderly and the very young. At least 20,000 people die from influenza and its complications each year in the United States.

An experimental vaccine sprayed as a fine mist into children's nostrils has been shown to protect not only against the strains of flu it was designed to cover, but also against a new strain that emerged through the spontaneous genetic changes to which flu viruses are prone. This experimental vaccine builds on NIH-supported work on the concept of a cold-adapted live virus vaccine – work that has been pursued since the mid-1970s by investigators in NIH's Laboratory of Infectious Diseases and their colleagues at the University of Michigan. A "cold-adapted," vaccine virus is one that grows well in the relatively cool environment of the mucosal tissues of the upper respiratory system – the place where flu virus attacks first. Since these viruses grow in the mucosal tissues, the vaccine has the advantage of stimulating mucosal as well as systemic immunity. The proof of the efficacy of this approach comes from NIH-sponsored clinical trials that tested a live attenuated, cold-adapted, trivalent (contains three different virus strains) influenza vaccine that is delivered into the body via a nasal spray. The children participating in the trial were 1 to 6 years old when the trial started. The trial targeted that age group because young children are two to three times more likely than adults to become ill with flu, and children frequently spread the virus to others.

Early reports from the first large clinical trial of this intranasal flu vaccine confirmed that the novel vaccine is highly effective. The trial started just prior to the 1996-1997 flu season. In its first year, the intranasal vaccine was over 90 percent effective against the two flu strains that circulated in the U.S. that winter (A/Wuhan/H3N2 and B/Harbin). The following fall, a new flu strain (A/Sydney/H3N2) emerged that was related to A/Wuhan/H3N2, but was unique enough to be considered a separate challenge to the body. In the second year of the trial, most of the children were revaccinated. However, because A/Sydney/H3N2 emerged so late, investigators were unable to update the experimental intranasal vaccine to include it. Nonetheless, the intranasal vaccine was 86% effective in protecting the children against A/Sydney during that year. This showed that the live attenuated, cold-adapted, intranasal influenza vaccine was broadly effective because it was capable of protecting against a strain not covered in the vaccine. Although the third flu strain chosen for inclusion in the intranasal vaccine, A/H1N1, did not circulate during the first two years of the study, blood tests of children vaccinated with the intranasal spray showed that the children also produced high levels of antibodies in response to A/H1N1, which is suggestive of a protective effect.

Edible Vaccine. Edible plants engineered to contain immune-stimulating vaccine components provide another novel approach for vaccine delivery. NIH-funded scientists, from Boyce Thompson Institute (BTI) for Plant Research at Cornell University and the University of Maryland School of Medicine in Baltimore, recently conducted the first human clinical trials of transgenic plant vaccines designed to

protect against infection with the Norwalk virus, a leading cause of gastrointestinal illness in the United States and much of the developed world.

In the study, a group of healthy adult volunteers ate two or three doses of transgenic, raw potato bio-engineered to contain an assemblage of protein from the Norwalk virus that served as the test vaccine. A separate group of volunteers served as controls and ate doses of ordinary, unaltered potatoes. Of the 20 volunteers who ate the transgenic potatoes, 19 (95 percent) developed an increased immune response to the Norwalk virus of some kind. The finding builds on earlier work that demonstrated that potato or tomato plants engineered to produce a component the *Escherichia coli* enterotoxin could induce antibodies against the toxin. They also found that the immune stimulating component was protected by the plant cells during digestion and remained active in the intestinal tract.

Not only have transgenic plants proved to be a potential means to safely deliver vaccines, but the plants could be produced locally and cheaply. Furthermore, homegrown vaccines would eliminate the problems of transporting traditional vaccines long distances without refrigeration. And because the vaccines are eaten, immunization would not require syringes and involve the discomfort and possibility of local infection associated with injections. A number of plant-based vaccines against other human diseases, such as rabies, the ulcer-causing *Helicobacter pylori*, and hepatitis B, have also been tested, with NIH support, in animals, with promising results.